PREPARATION, INSILICO, AND ANTI OXIDANT STUDIES OF OXYGEN AND SULPHUR CONSISTING 1, 5 -DI AZA BICYCLIC COMPOUNDS

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Abstract: Ethylene bridge contained compounds with two nitrogen's along with oxygen / sulphur enhances the biological activity, hence we designed a series of newer 1,5 Di Aza bicyclic compounds (**I–XII**). They prepared from Pyrmidone and Thiopyrimidones reaction with dibromo ethane using ethyl acetate solvent in presence of cesium carbonate. Among the twelve compounds, two compounds- **I&VII** formed with 89 & 88 % of yield; Insilico studies with IPASS&OSIRIS software results that titled compounds are having good drug likeness and drug score. Antioxidant activity (DPPH inhibition % + Standard deviation) of titled compounds compared with Ascorbic acid, which reveals that activity excellent for compound-**VI**, good for compound-**II**, & **X**.

Keywords: Thiopyrimidone, 1,5 Di Aza bicyclic compounds, Anti oxidant activity, DPPH method

INTRODUCTION

From the reaction of nitro-δ-keto esters and various diamines with partial intramolecular mechanism leads to produce the nitrolactam contained diaza bicyclo compounds with good yields [1]. A newer catalyst polyurethane synthesized from the 1,5-diazabicyclo[4.3.0]non-5-ene

(DBN) and substituted isocyanates [2]. Nano-SiO2 / 1,5-diazabicyclo [4.3.0] non-5-en [DBN] prepared, analysed and used as a different nanocatalyst to prepare derivatives of tetrahydrobenzopyran [3]. Diazabicyclohexane compounds (DABHCs) are efficient liquid hypergolic components. The LD50 expected values of these compounds indicate that grade four with slight toxic, and grade five with non-toxic according to globally recognized system [4].

Conformationally strained molecules has biological activity, they has crucial role in the pharmaceutical chemistry [5]. A molecule with more number of binding sites which is interacts with the target acting as good pharmacophore [6].

Polypeptide with thirty-seven aminoacids as a set of calcitonine indicated interms of Calcitonin gene-related peptide (CGRP), which has a crucial task to reduce the migraine [7, 8]. CGRP receptor, which binds to the Calcitonin Gene-Related Peptide it is known as G-protein coupled receptor having seven transmembrane element Calcitonine Receptor Like Receptor and Receptor Activity Modifying Protein [9, 10]. Substituted 1,4-diazabicyclo[3.3.1]nonane compounds prepared and tested for binding affinity and invivo activities towards Dopamine transporter (DAT), serotonin transporter, norepinephrine transporter in the brain [11]. 3,8-diazabicyclo[3.2.1]octanes in vitro study of the model 3,8-bis[2-(3,4,5-trimethoxyphenyl)pyridyl-4-yl)methylpiperazine prepared and tested the growth of the cell against leukemia, certain solid tumors [12].

1,4-diazabicyclo[2.2.2]octane series prepared, among series two compounds are showed good result for antibacterial activity. For antiviral activity of titled compounds one compound has better activity [13]. 3,7diazabicyclononane known as (bispidine) it is observed in many natural alkaloids, among them one of the most important alkaloid is tetracyclic alkaloid. These compounds are having the various biological activities, applicable as a ligand, as a catalytic activity, and also in polymers preparation [14]. The DPPH method is a simple and quick way, to test the possible antioxidant activity of the substances and they regress the dental bleaching problems [15]. Copper catalysed, isoxazole conjugated chromene twelve derivatves prepared with good yields. Two compounds are with anti oxidant activity, three compounds are having anti bacterial activity [16]. The compounds with antioxidant nature inhibit the production of oxidative species and lead to reduce diseases due to the age factor. The Antioxidant activity helping indirectly on the Ageing research (c. elegans in vivo study) on the worms [17]. Thirty

different plant extractions are tested for antioxidant properties by DPPH method, Oak, Pine, and Cinnamon extractions are consisting more acivity [18]. Various substitutions consisting of Ethenyl indoles have been prepared and checked for their anti-oxidant activity.

Electron donating groups like hydroxyl substituted have more activity than withdrawing groups compared to vitamin E [19]. White mulberrie plants various parts extractions containing Phenols, flavonoids are having anti oxidant activity, evaluated it with DPPH method [20].

RESULTS AND DISCUSSION

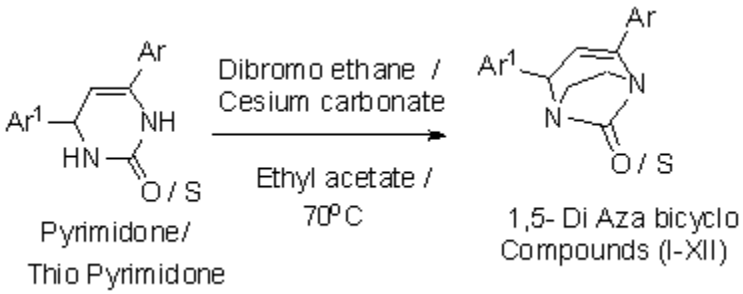
Twelve Biologically active diazabicyclo compounds consisting aromatic / heterocyclic groups, which are prepared from substituted pyrimidone / thio pyrimidones reaction with 1,2 di bromo ethane in presence of cesium carbonate which acts as a base, ethyl aceatate as a solvent at 70 ^{o}C with a simple procedure.

The Compound -**I** & **VII** with two-phenyl group yielded 89% & 88%. The percentage of yield for compound -**II** is 90% it consists styryl, chloro phenyl groups. Drug score/drug likeness good for the Compound-**II** which is consisting chlorophenyl, styryl group's these predictions done by OSIRIS software. Among the series, mainly antmitotic, polarisation stimulant activity prediction performed by the IPASS software. Anti oxidantal activity of titled compounds revealed that compound - **VI** with thiophene, chromenyl groups has more active than the reference ascorbic acid.

EXPERIMENTAL

All the chemicals, reagents, and solvents utilised in the synthesis were purchased from Sigma, Alfa Aeser, and Spectrochem at the highest purity levels and utilised without additional purification. Agilent Cary 630 FT-IR spectrometer used to record IR spectra. A commercial LCQ ion trap mass spectrometer (Thermo Finnigan, SanJose, CA, USA) coupled with an ESI source was used to collect mass spectral data. Bruker was used to record ^{1}HNMR spectra.

Scheme 1:



Synthesis of Di Aza Bicyclo compounds (I-XII)

General synthetic protocol of 1,5 Diazabicyclo compounds (I–XII): The Reaction of Pyrimidones / Thiopyrimidones with dibromo ethane in ethylacetate solvent using cesium carbonate as base, heating the mixture at 70^{o}C, the progress of the reaction checked with TLC. After three hours, the reaction mixture poured in a crushed ice contained beaker and solid separated, filtered the precipitate, dried the mixture, and recrystallised from ethanol to get pure titled compounds.

(1R,5S)-2,4-diphenyl-1,5-diazabicyclo[3.2.1]oct-2-en-8-one (I): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, C$\underline{H}_2$, t), 3.7 (2H, C$\underline{H}_2$,t,), 5.6(1H,=C$\underline{H}$, s), 6.1 (1H, N-C$\underline{H}$, s), 7.2 – 7. 7 (10H, Ar-H, m). %Yield: 89, Chemical Formula $C_{18}H_{16}N_2O$. m/z: 329.15 [M+$^{+}$$NH_4Cl$].

(1R,5S)-2-(4-chlorophenyl)-4-((E)-styryl)-1,5-diazabicyclo[3.2.1]oct-2-en-8-one (II): ^{1}H NMR (DMSO, δ, ppm) :3.4(4H, -C$\underline{H}_2$-C$\underline{H}_2$-,t), 4.9(1H, C$\underline{H}$-N, t), 5.6(1H, =C$\underline{H}$, s), 6.2(2H,-C$\underline{H}$=C$\underline{H}$-, dd), 7.2 – 7.44 (9H, m,Ar). % of yield: 90, Chemical Formula: $C_{20}H_{17}ClN_2O$, m/z: 336.10.

(1S,5R)-2-(2-oxo-2H-chromen-3-yl)-4-(4-oxo-4H-chromen-3-yl)-1,5-diazabicyclo[3.2.1]oct-2-en-8-one (III): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, -C$\underline{H}_2$, t), 3.7 (2H, -C$\underline{H}_2$,t,), 5.6(1H, =C$\underline{H}$, s), 6.1 (1H, N-C$\underline{H}$, s),7.4 – 7.8 (10H, Ar-H, m).%Yield: 87, Chemical Formula: $C_{24}H_{16}N_2O_5$, Exact Mass: m/z: 412.11.

(1R,5S)-2-(2-chloroquinolin-3-yl)-4-(2-oxo-2H-chromen-3-yl)-1,5-diazabicyclo[3.2.1]oct-3-en-8-one (IV): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, C$\underline{H}_2$, t), 3.7 (2H, C$\underline{H}_2$,t,), 5.6(1H, =C$\underline{H}$, s), 6.1 (1H, N-C$\underline{H}$, s), 7.4 – 7.8 (8H, Ar-H, m), 8.2(2H). %Yield: 86, Chemical Formula: $C_{24}H_{16}ClN_3O_3$, m/z: 429.09.

(1R,5S)-2-(2-butyl-4-chloro-1H-imidazol-5-yl)-4-(2-oxo-2H-chromen-3-yl)-1,5-diazabicyclo[3.2.1]oct-3-en-8-one (V): ^{1}H NMR (DMSO, δ, ppm) : 0.9(3H, C*H*$_3$, t), 1.3(2H, C*H*$_2$, m), 1.6(2H, C*H*$_2$, m), 2.8(2H, C*H*$_2$, t), 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 5.6(1H, =C*H*, s), 6.1 (1H, N-C*H*, s), 7.4 – 7.8 (5H, Ar-H, m), 13(1H,N*H*, imidazole). %Yield: 86, Chemical Formula: $C_{22}H_{21}ClN_4O_3$, m/z: 424.13.

(1S,5R)-2-(2-oxo-2H-chromen-3-yl)-4-(thiophen-2-yl)-1,5-diazabicyclo[3.2.1]oct-2-en-8-one (VI): ^{1}H NMR (400 MHz, (DMSO, *δ, ppm*): 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 5.6(1H, =C*H*, s), 6.1 (1H, N-C*H*, d), 7.0(2H, d, thiazole) 7.3(1H,s, thiazole), 7.5 – 7.8 (5H, Ar-H, m). %Yield: 85, Chemical Formula: $C_{19}H_{14}N_2O_3S$, m/z : 350.07.

(1R,5S)-2,4-diphenyl-1,5-diazabicyclo[3.2.1]oct-3-ene-8-thione (VII): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 5.6(1H,=C*H*, s), 6.6 (1H, N-C*H*, s), 7.2 – 7. 7 (10H, Ar-H, m). %Yield: 88, Chemical Formula: $C_{18}H_{16}N_2S$, m/z : 292.10

(1R,5S)-2-(4-chlorophenyl)-4-((E)-styryl)-1,5-diazabicyclo[3.2.1]oct-2-ene-8-thione (VIII): ^{1}H NMR (DMSO, δ, ppm) : 3. 6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 4.1 (1H, N-C*H*, s), 6.6 (1H, =C*H*, s), 6.7(1H ,=C*H*, ,d), 6.8(1H,= C*H*, d), 7.2 – 7.40 (9H, Ar-H, m). %Yield: 87, Chemical Formula: $C_{20}H_{17}ClN_2S$, m/z: 352.08.

3-((1R,5S)-4-(4-oxo-4H-chromen-3-yl)-8-thioxo-1,5-diazabicyclo[3.2.1]oct-2-en-2-yl)-2H-chromen-2-one (IX): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 4.1 (1H, N-C*H*, s), 5.6(1H, =C*H*, s), 7.1(1H, =C*H*, s), 7.5 (1H, C=C*H*, s), 7.6– 7.8 (8H, Ar-H, m). %Yield: 84, Chemical Formula: $C_{24}H_{16}N_2O_4S$, m/z : 428.46.

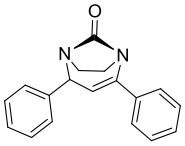
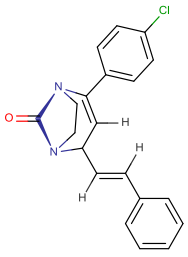
3-((1R,5S)-4-(2-chloroquinolin-3-yl)-8-thioxo-1,5-diazabicyclo[3.2.1]oct-2-en-2-yl)-2H-chromen-2-one (X): ^{1}H NMR (DMSO, δ, ppm) : 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 4.5 (1H, N-C*H*, s), 5.6(1H, =C*H*, s), 7.5 (1H, C=C*H*, s), 7.7– 8.0 (8H, Ar-H, m),8.2(1H, =C*H*, s). %Yield: 87, Chemical Formula: $C_{24}H_{16}ClN_3O_2S$, m/z: 445.07.

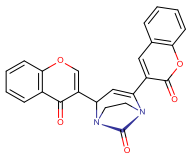
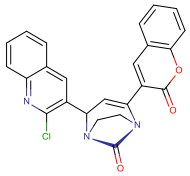
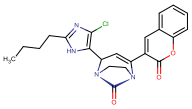
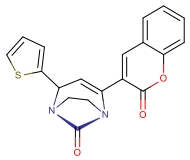
3-((1S,5R)-4-(2-butyl-4-chloro-1H-imidazol-5-yl)-8-thioxo-1,5-diazabicyclo[3.2.1]oct-2-en-2-yl)-2H-chromen-2-one (XI): ^{1}H NMR (400 MHz, (DMSO-d_6, *δ, ppm*): 0.9(3H, -C*H*$_3$, t), 1.3(2H, -C*H*$_2$, m), 1.6(2H,-C*H*$_2$, m), 2.9(2H, -C*H*$_2$, t), 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 4.5 (1H, N-C*H*,

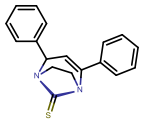
s), 5.6(1H, =C*H*, s), 7.5 (1H, C=C*H*, s), 7.5– 7.8 (4H, Ar-H, m), 13.0(1H, N*H*, br). %Yield: 84, Chemical Formula: $C_{22}H_{21}ClN_4O_2S$, m/z: 440.11.

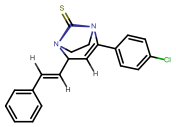
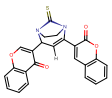
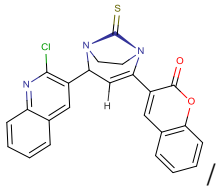
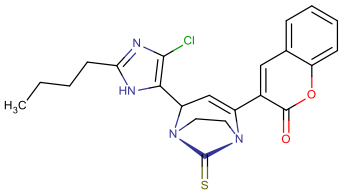
3-((1S,5R)-4-(thiophen-2-yl)-8-thioxo-1,5-diazabicyclo[3.2.1]oct-2-en-2-yl)-2H-chromen-2-one (XII): ^{1}H NMR (400 MHz, (DMSO-d_6, δ, *ppm*): 3.6 (2H, C*H*$_2$, t), 3.7 (2H, C*H*$_2$,t,), 4.5 (1H, N-C*H*, s), 5.9(1H, =C*H*, s), 6.8(1H, Ar, d), 6.9(1H, Ar,t), 7.4 (1H, C=C*H*, s), 7.5(1H, =CH,s), 7.6– 7.8 (4H, Ar-H, m). %Yield: 86, Chemical Formula: $C_{19}H_{14}N_2O_2S_2$, m/z: 366.05.

Table 1: ***In silico*** **studies of bicycle compounds (I–XII)**

Compound structure & number / Drug likeness / Drug score by OSIRIS software	**IPASS Prediction**
I)  /3.5 / 0.97	1) Antimitotic 2) Glycosylphosphatidylinositol phospholipase D inhibitor 3) Nicotinic alpha6beta3beta4alpha5 receptor antagonist 4) Nicotinic alpha2beta2 receptor antagonist 5) Polarisation stimulant
II)  / 5.04 / 0.9	1) Phobic disorders treatment 2) Glycosylphosphatidylinositol phospholipase D inhibitor 3) Muscular dystrophy treatment 4) Gluconate 2-dehydrogenase (acceptor) inhibitor 5) 5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
III)	1) Histidine kinase inhibitor

 / 2.73 / 0.9	2) CYP2A11 substrate 3) HIF1A expression inhibitor 4) Aldehyde oxidase inhibitor 5) Polarisation stimulant
IV)  /2.5/0.6	1) CF transmembrane conductance regulator agonist 2) CYP2A11 substrate 3) Polarisation stimulant 4) Antimitotic 5) pasmolytic, urinary
V)  / -2.4/0.4	1) Imidazoline I1 receptor agonist 2) CYP2A11 substrate 3) polarisation stimulant 4) Complement inhibitor 5)CF transmembrane conductance regulator agonist
VI)  /2.9/0.8	1)Anaphylatoxin receptor antagonist 2) Spasmolytic, urinary 3) Muscular dystrophy treatment 4) Complement factor D inhibitor 5) CYP2A11 substrate

VII)  / 3.05/0.78	1)Antimitotic 2) Chloride peroxidase inhibitor 3) Nicotinic alpha6beta3beta4alpha5 receptor antagonist 4)Glycosylphosphatidylinositol phospholipase D inhibitor

	5) (S)-6-hydroxynicotine oxidase inhibitor
VIII)  /2.47/0.53	1) Phobic disorders treatment 2) Glycosylphosphatidylinositol phospholipase D inhibitor 3) Chloride peroxidase inhibitor 4) Antineurotic 5) 5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
IX)  / 4.33/0.49	1) Histidine kinase inhibitor 2) CYP2A11 substrate 3) HIF1A expression inhibitor 4)Antineoplastic 5) Serine protease unspecified inhibitor.
X)  / 4.05/0.41	1) CF transmembrane conductance regulator agonist 2) CYP2A11 substrate 3) Serine protease unspecified inhibitor 4) Antimitotic 5) Spasmolytic, urinary
XI)  / -0.83/0.4	1) Imidazoline I1 receptor agonist 2) Serine protease unspecified inhibitor 3)CYP2A11 substrate 4) Complement inhibitor 5) Antiviral (Rhinovirus)
XII)	1)Anaphylatoxin receptor antagonist 2)Spasmolytic, urinary 3) Complement factor D inhibitor 4) CYP2A11 substrate

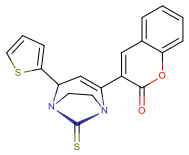
 / 4.51/0.61	5) PfA-M1 aminopeptidase inhibitor

Table-2: **Antioxidant activity of compounds (I–XII) determined by the DPPH method**

	At 517 nm wave length (DPPH inhibition % + Standard deviation)
compound I	5.33+0.01
compound II	4.93+0.02
compound III	22.29+0.02
compound IV	12.62+0.02
compound V	40.04+0.02
compound VI	3.55+0.01
compound VII	21.50+0.04
compound VIII	20.91+0.05
compound IX	12.43+0.02
compound X	4.54+0.02
compound XI	12.43+0.01
compound XII	5.33+0.01
Ascorbic acid	4.73+0.01

Antioxidantal study: The titled compounds **(I–XII)** were tested for their *in vitro* antioxidant activity by 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay method in this methanol (95%) as a blank, DPPH solution as a control and Ascorbic acid as a reference. In this work anti oxidant procedure followed from reference [16]. The absorbance was measured at wavelength 517 nm.

CONCLUSION

In this work newer 1,5 di aza bicyclic compounds (**I-XII**) were prepared with easy procedure and two compounds formed with good yields. *Insilico* studies resluts of these compounds shows

they can act as Polarisation stimulant, Glycosylphosphatidylinositol phospholipase D inhibitor. Invitro anti oxidant activity indicates one compound has excellent activity. In future, we are planning for invivo ageing studies on titled compounds.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that this research work does not contain any studies involving human participants or animal.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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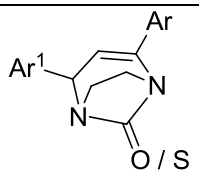
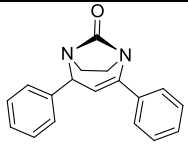
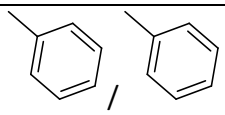
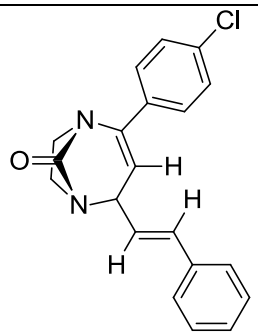
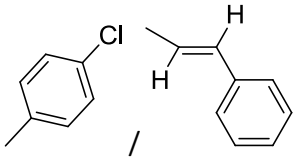
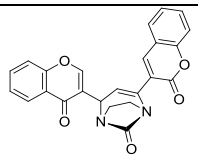
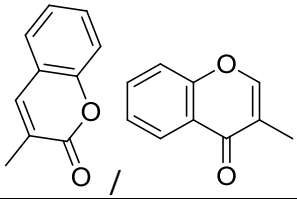
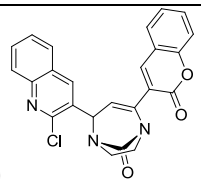
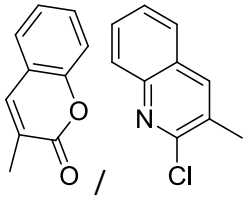
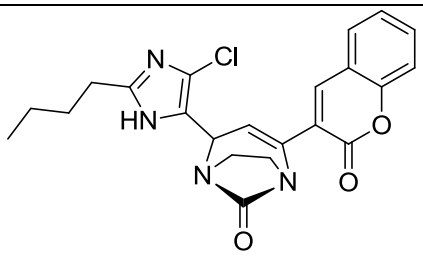
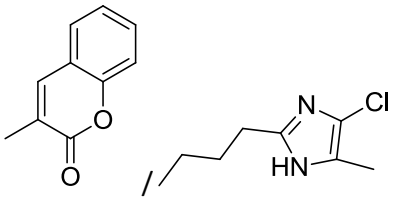
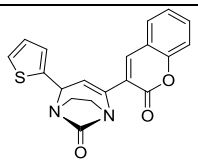
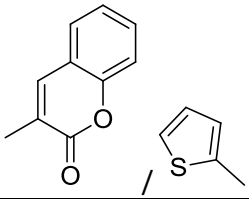
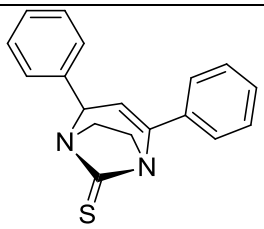
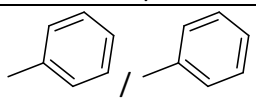
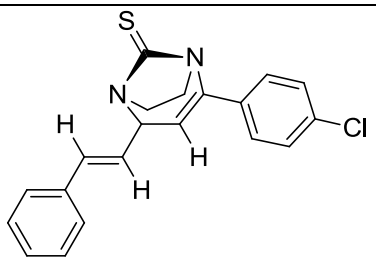
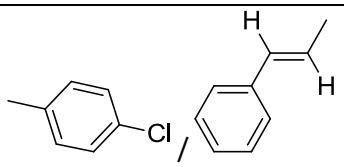
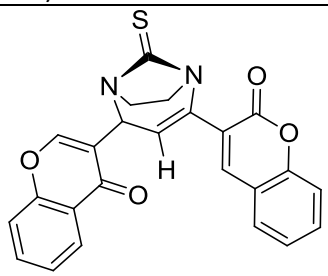
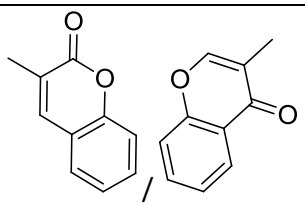
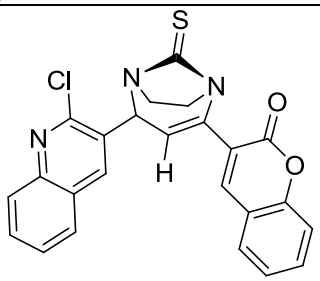
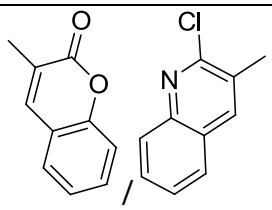
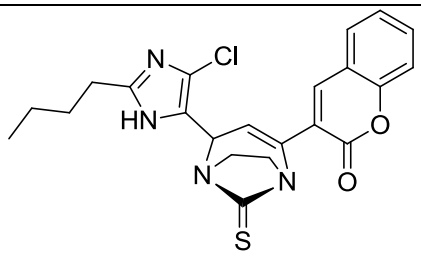
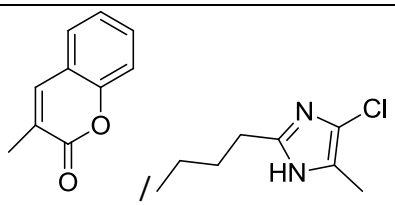
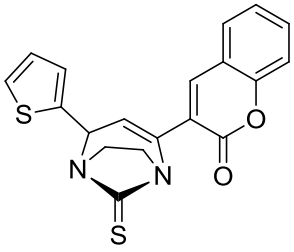
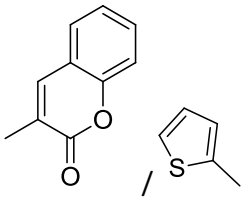
Supplementary data

	Ar / Ar[1]
I) 	

II) 	
III) 	
IV) 	
V) 	
VI) 	
VII) 	

 VIII)	
 IX)	
 X)	
 XI)	
 XII)	

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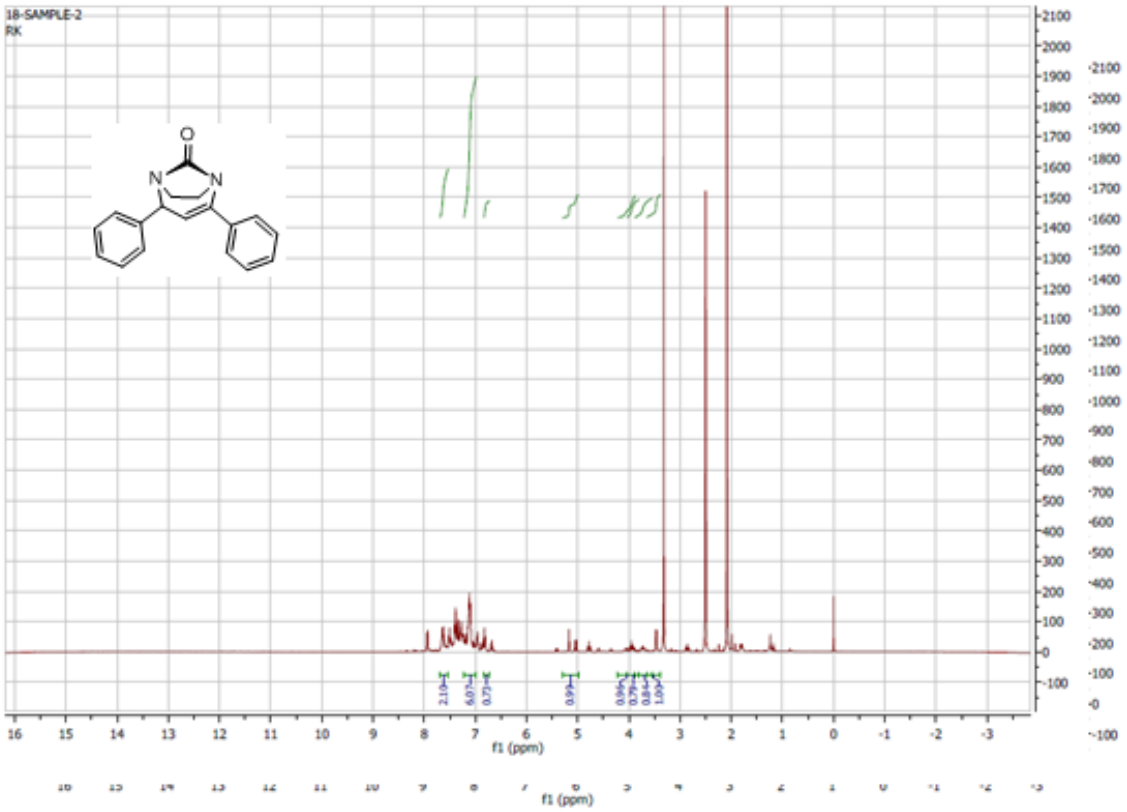

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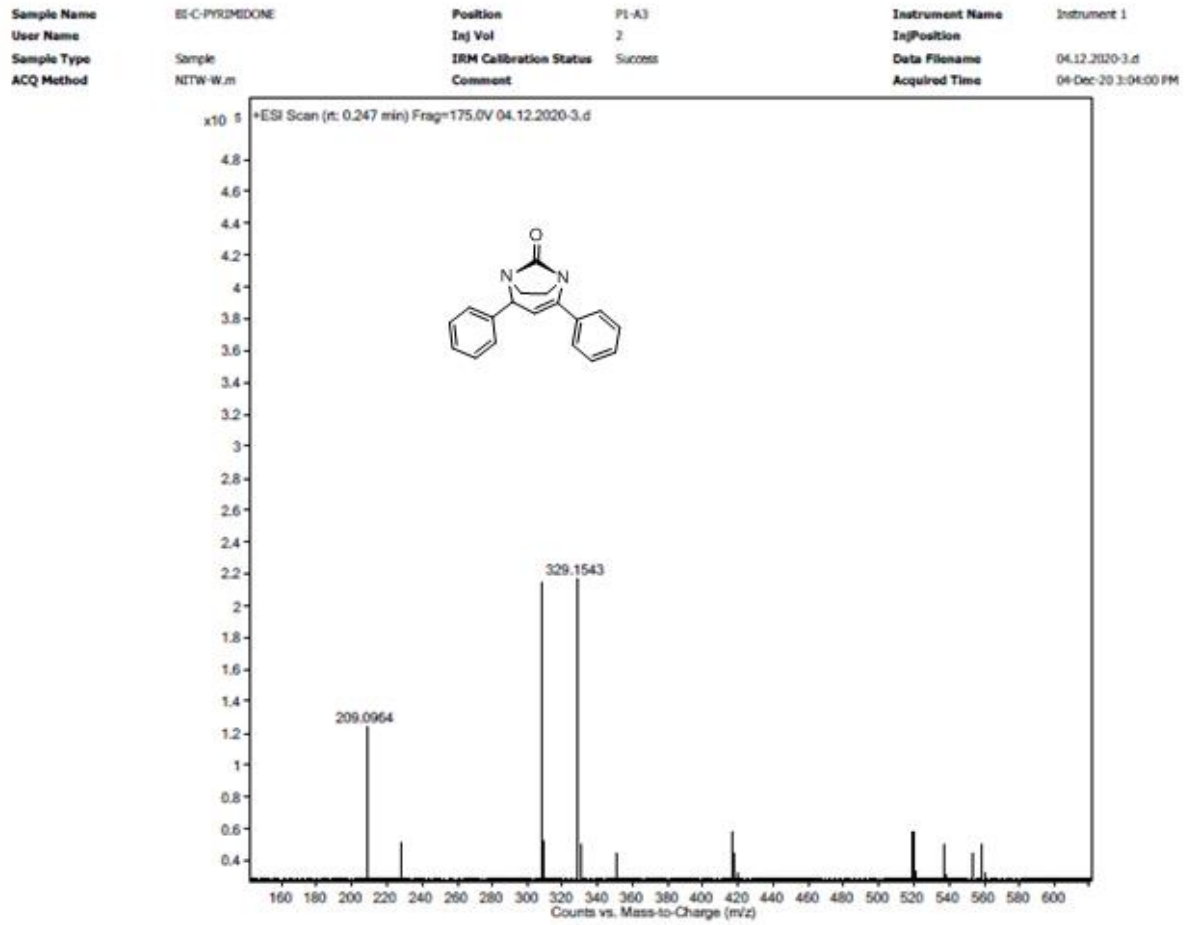
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Counts vs. Mass-to-Charge (m/z)

^{1}H NMR OF COMPOUND 2: