molecules

Synthesis of New Pyrazolo[3,4-*d*]pyrimidine Derivatives: NMR Spectroscopic Characterization, X-Ray, Hirshfeld Surface Analysis, DFT, Molecular Docking, and Antiproliferative Activity Investigations

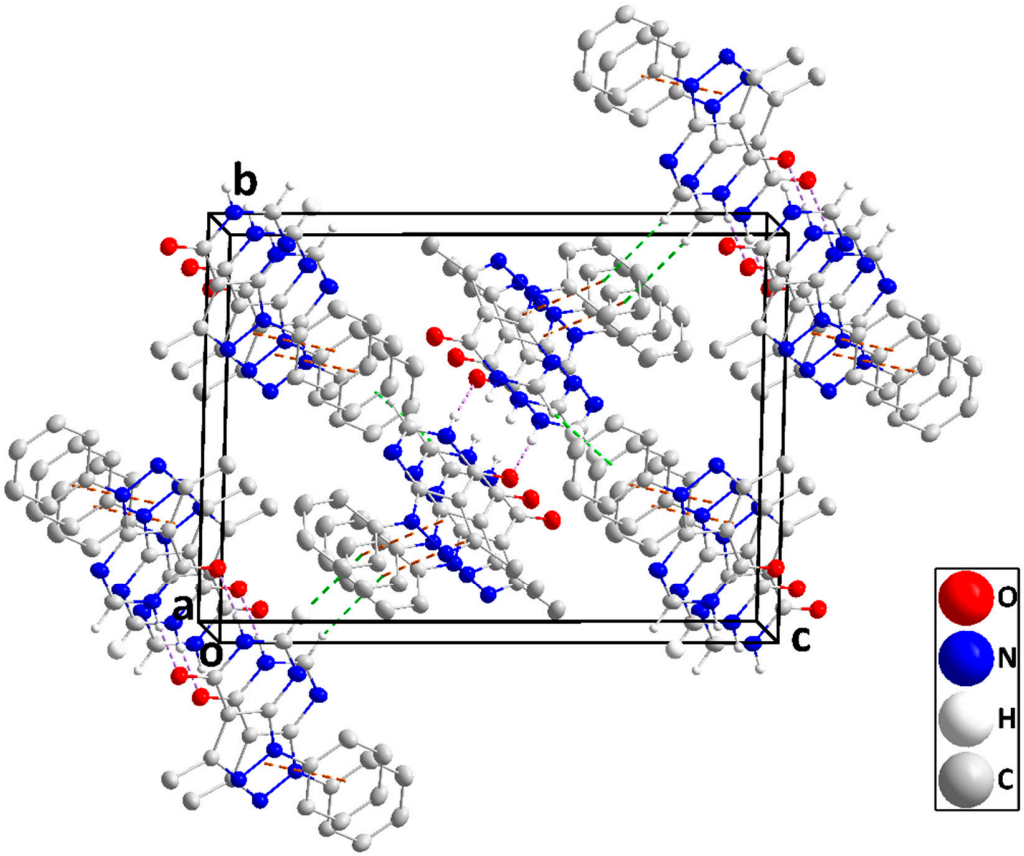
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7 Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia; mhefnawy@ksu.edu.sa
8 Department of Chemistry, Tulane University, New Orleans, LA 70118, USA; joelt@tulane.edu
* Correspondence: anouarelhassane@yahoo.fr

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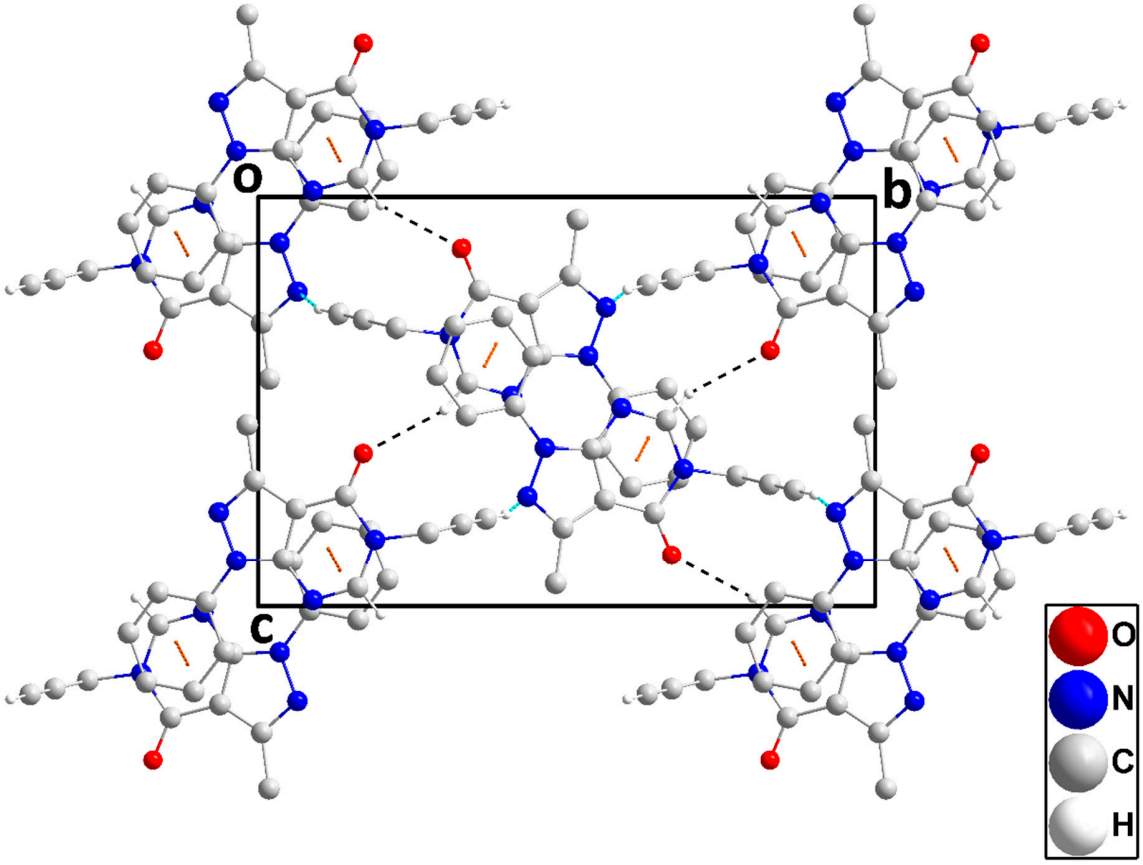
Figure S1

Perspective view of the packing with N—H···O hydrogen bonds and C—H···π(ring) and π-stacking interactions depicted, respectively, by violet, green, and orange dashed lines. Non-interacting hydrogen atoms are omitted for clarity.



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Figure S2
Packing viewed along the *a*-axis direction with intermolecular interactions depicted in Figure 4.



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Figure S3
Packing viewed along the *c*-axis direction with intermolecular interactions depicted in Figure 4.

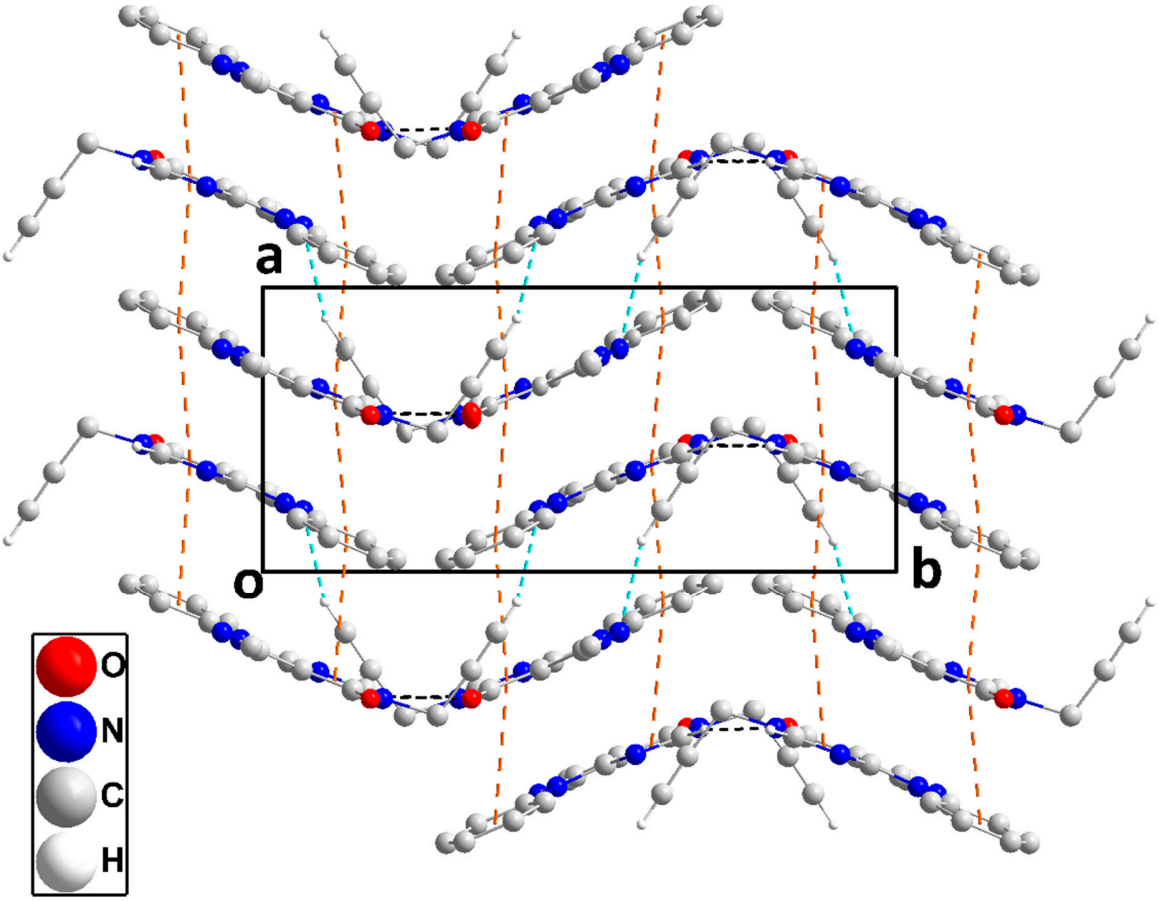
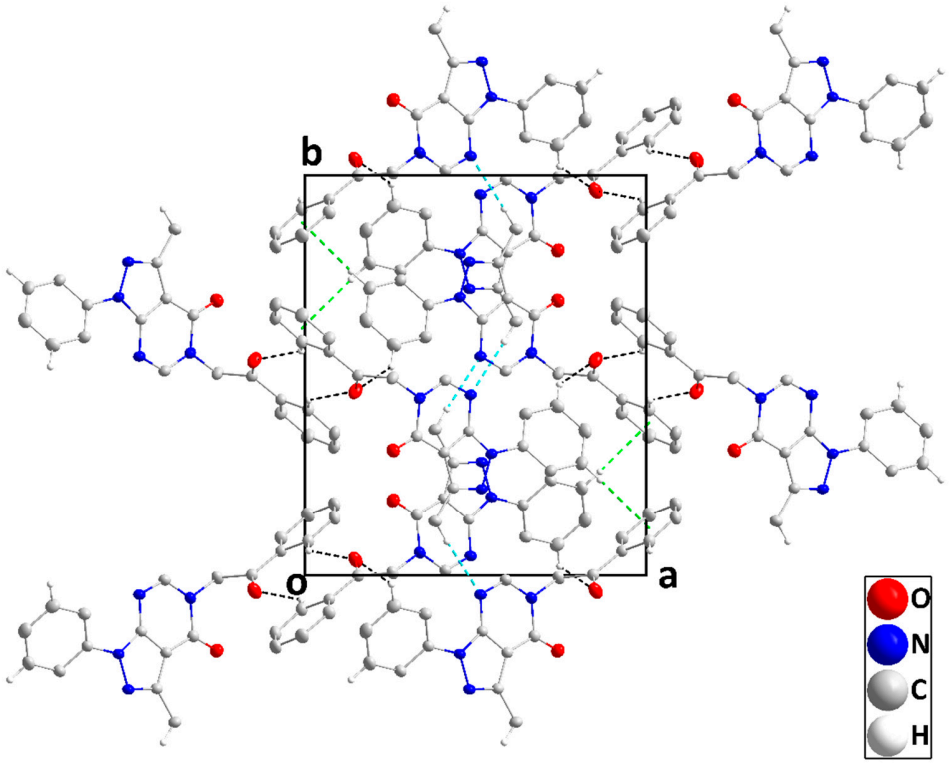


Figure S4

Packing viewed along the *b*-axis direction. C—H···O and C—H···N hydrogen bonds are depicted, respectively, by black and light blue dashed lines while C—H···π(ring) interactions are depicted by green dashed lines. Non-interacting hydrogen atoms are omitted for clarity.



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Figure S5
^{1}H NMR spectrum of compound **P1**.

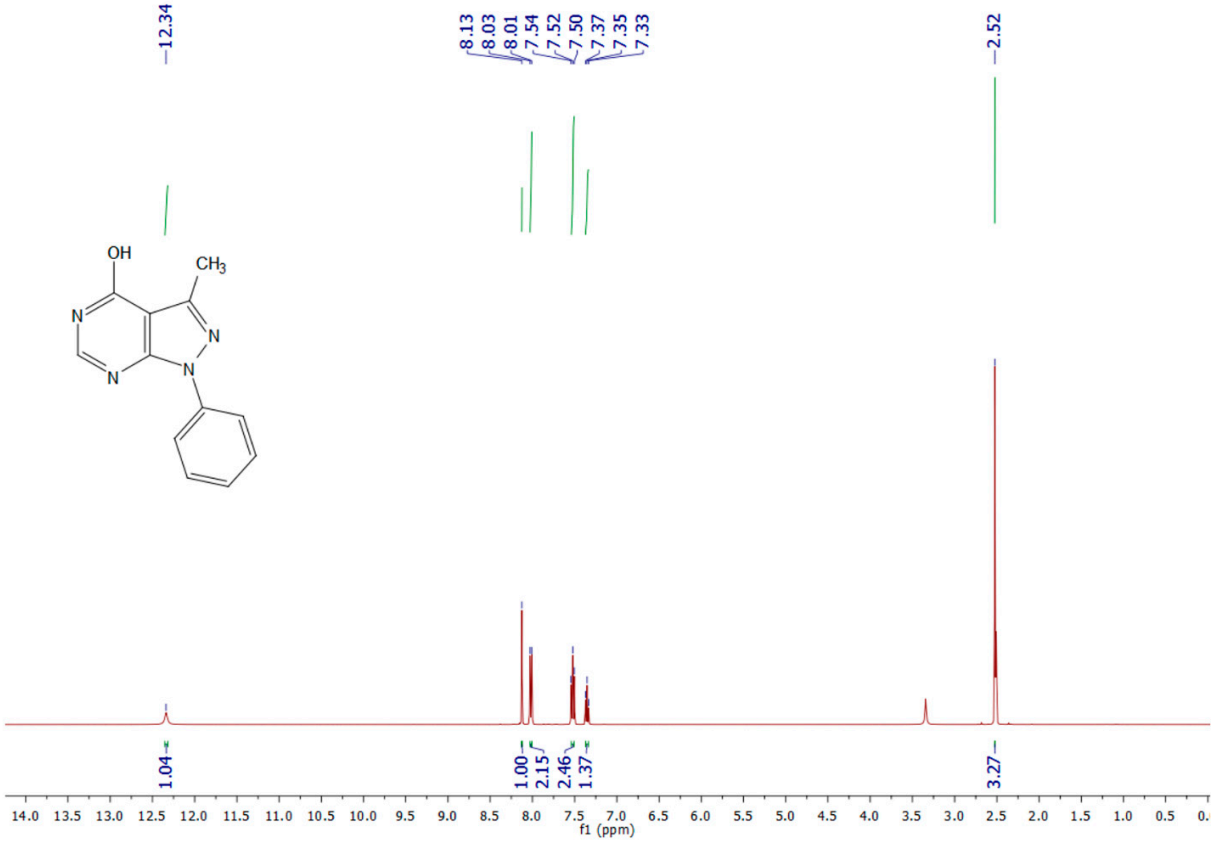
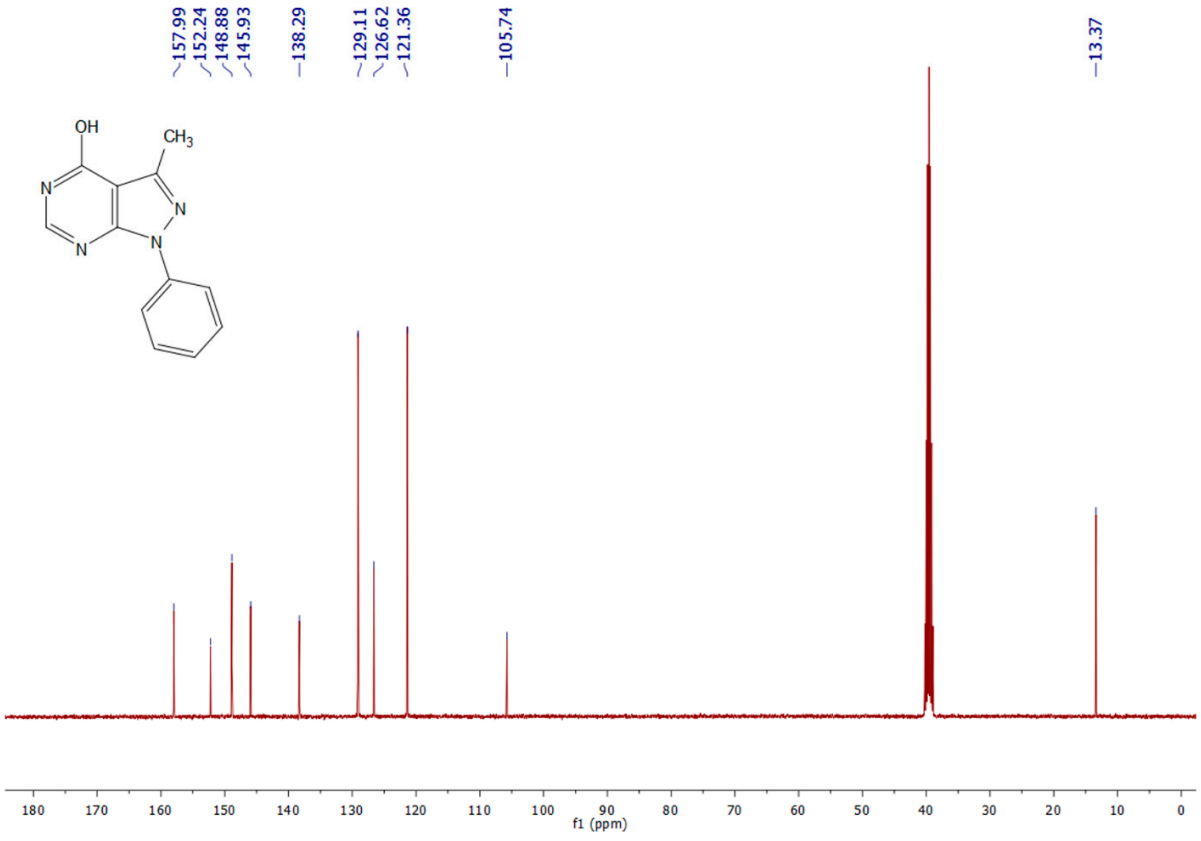
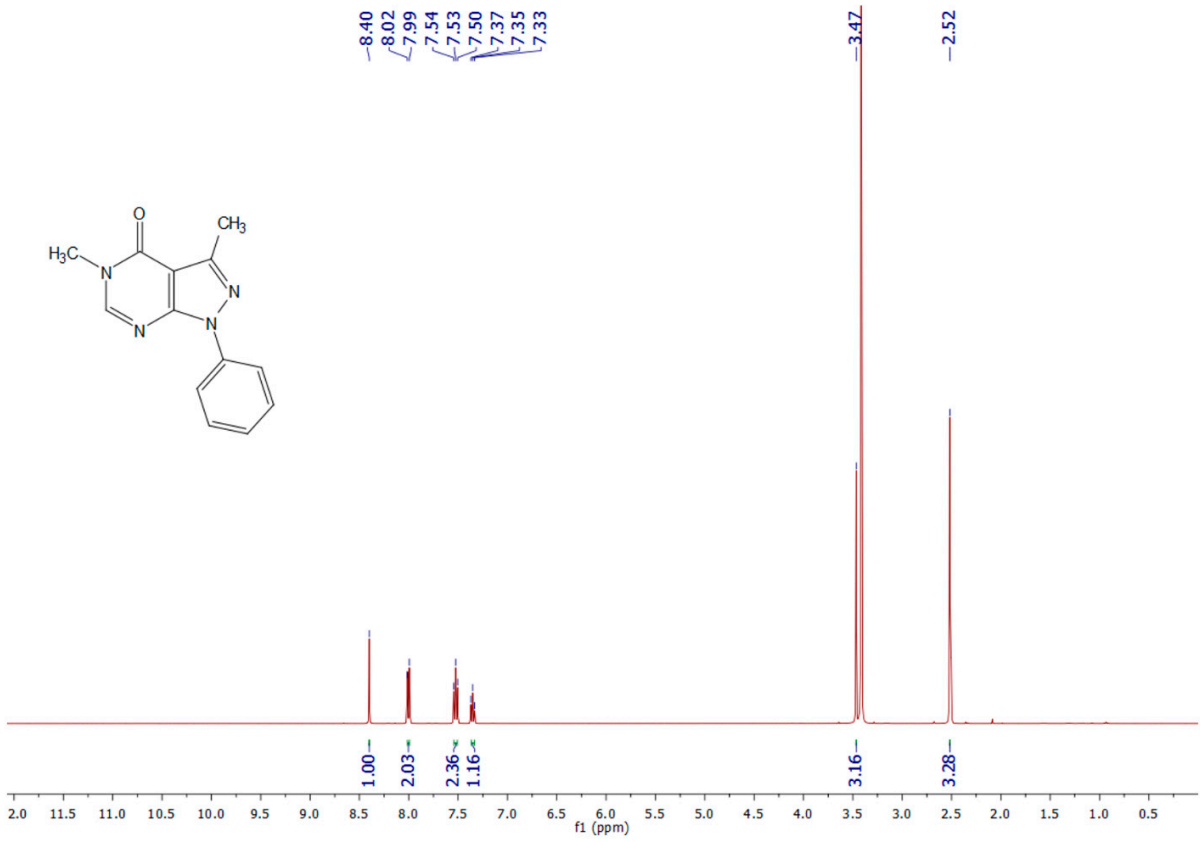


Figure S6
^{13}C NMR spectrum of compound **P1**.



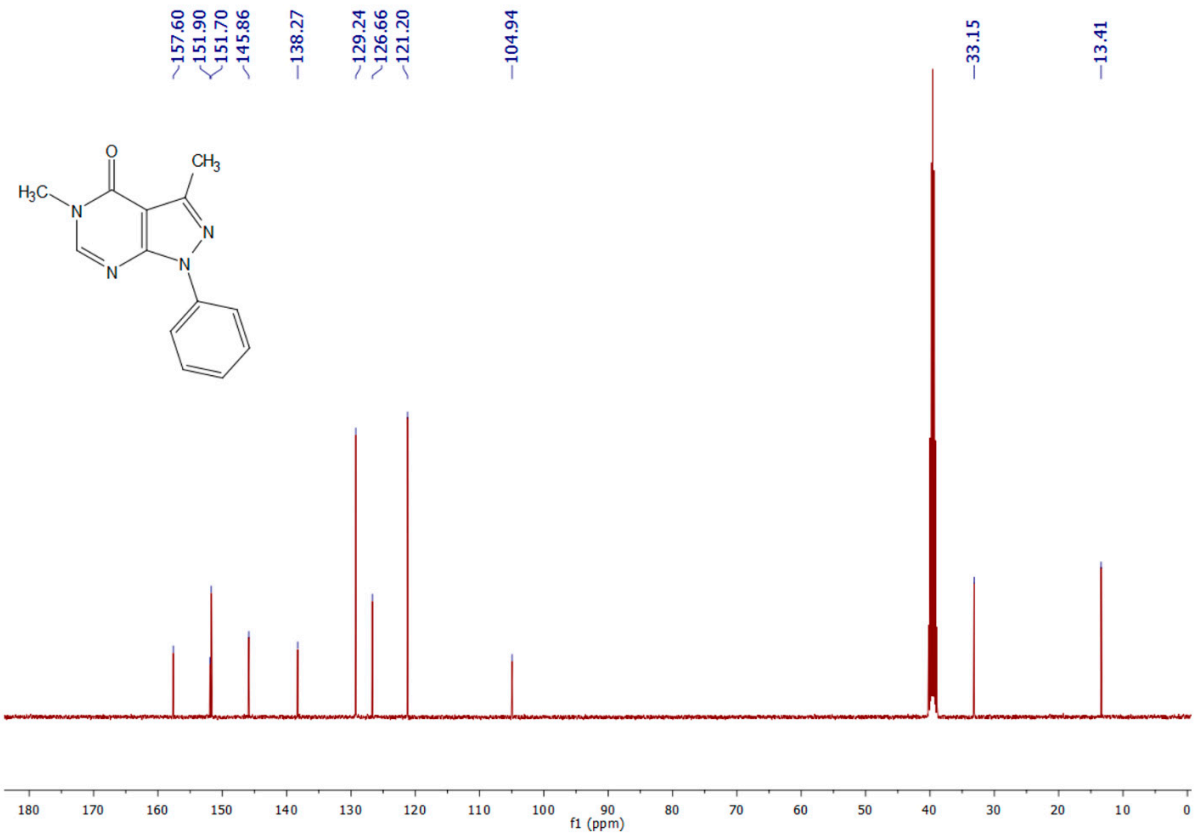
molecules

Figure S7
^{1}H NMR spectrum of compound **P2**.



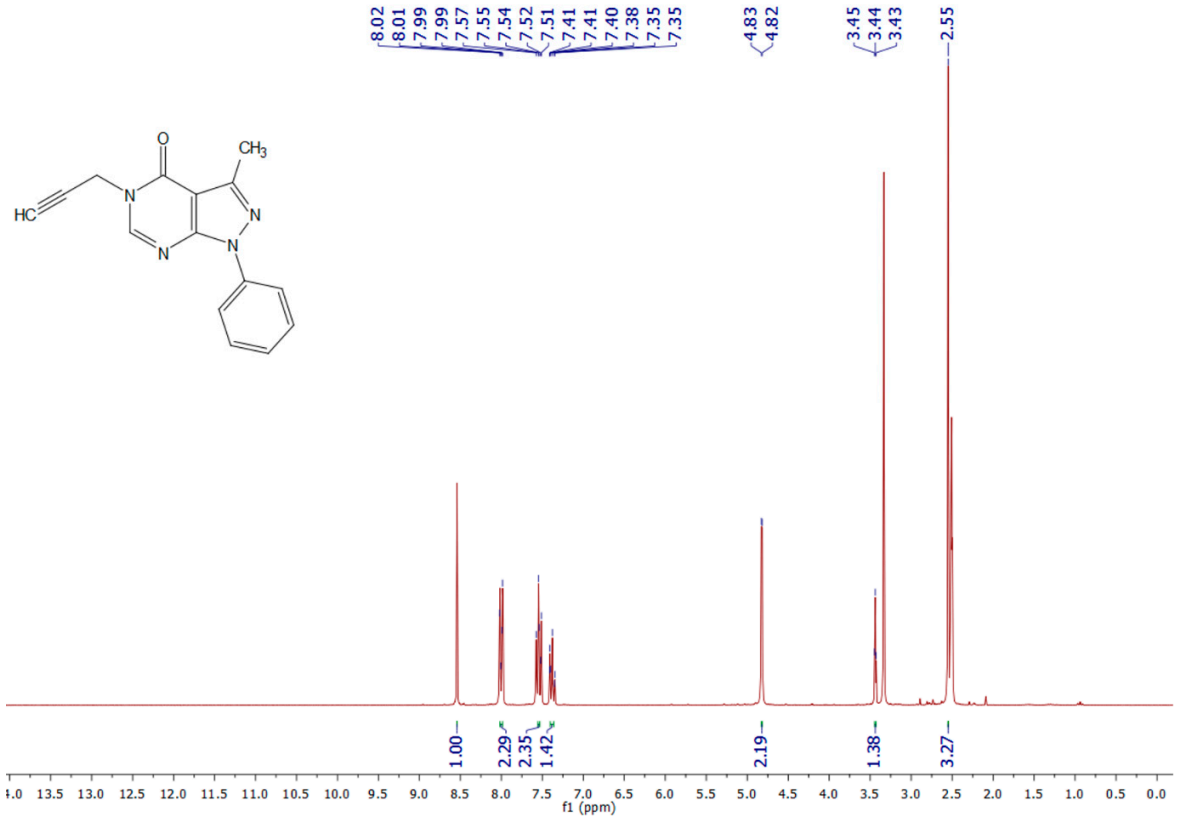
molecules

Figure S8
^{13}C NMR spectrum of compound P**2**.



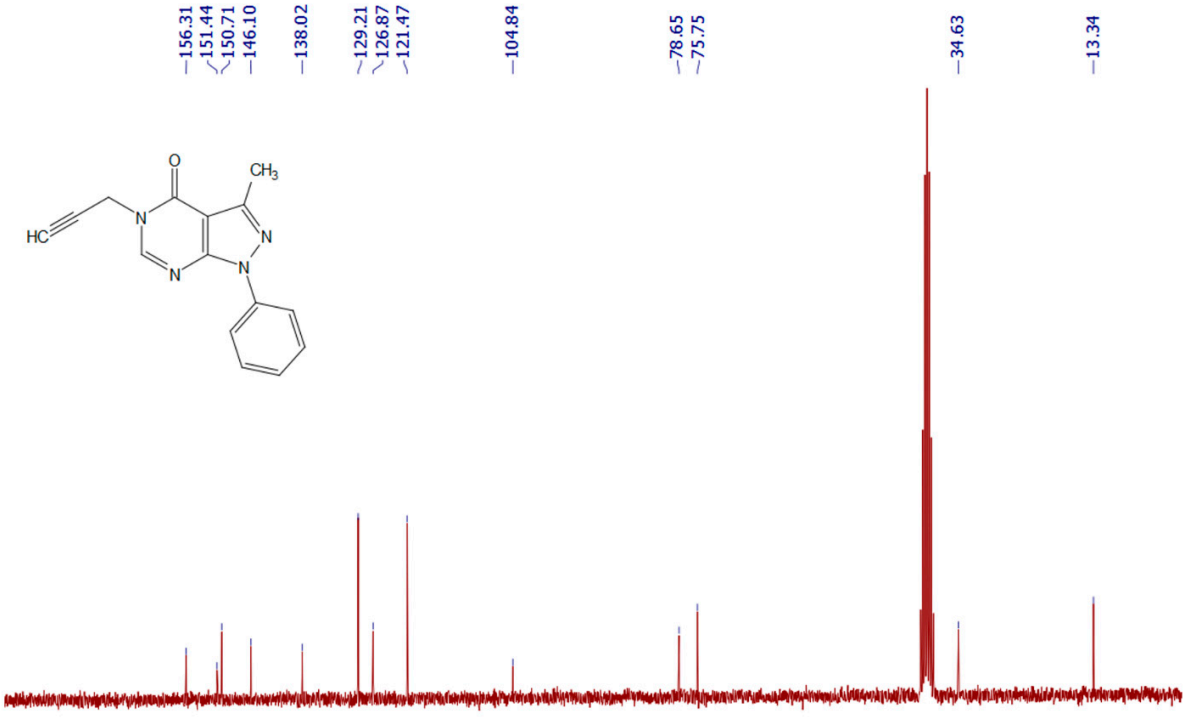
molecules

Figure S9
^{1}H NMR spectrum of compound **P3**.



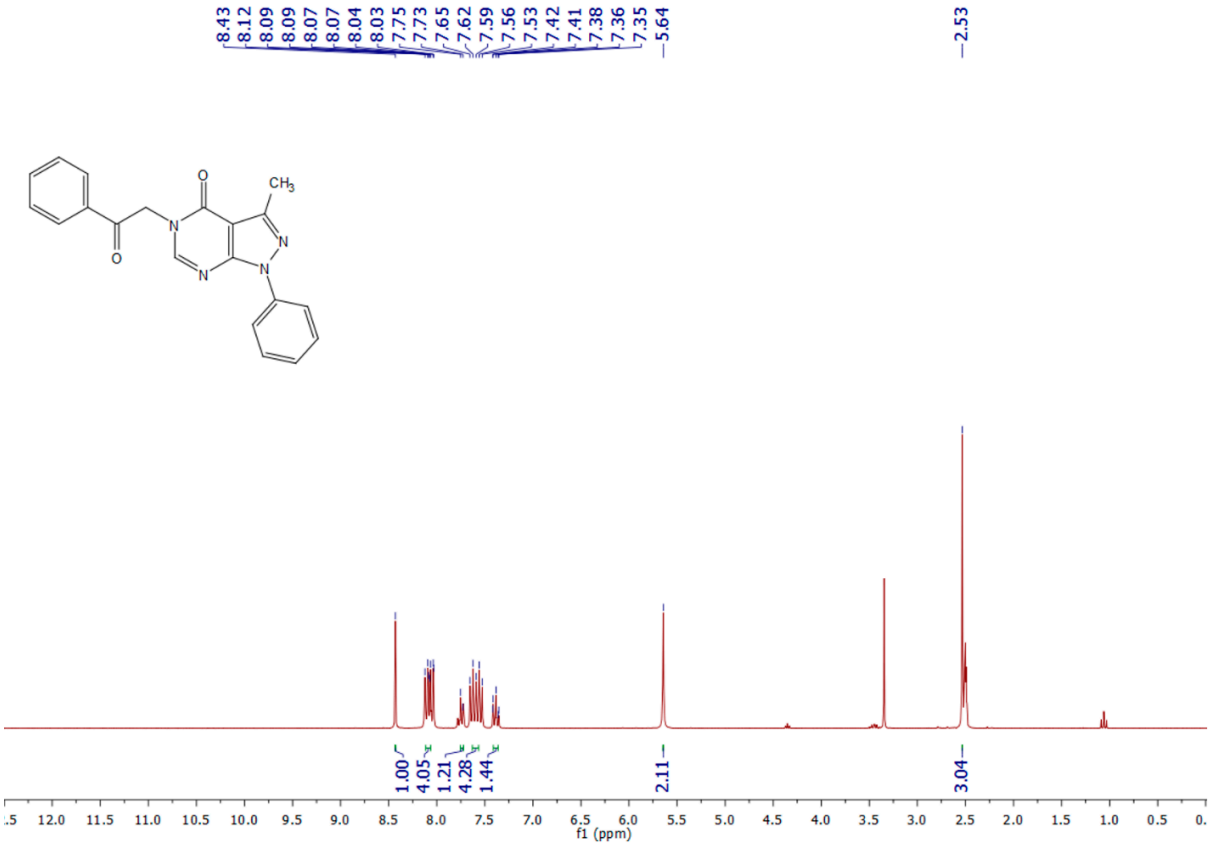
molecules

Figure S10
^{13}C NMR spectrum of compound **P3**.



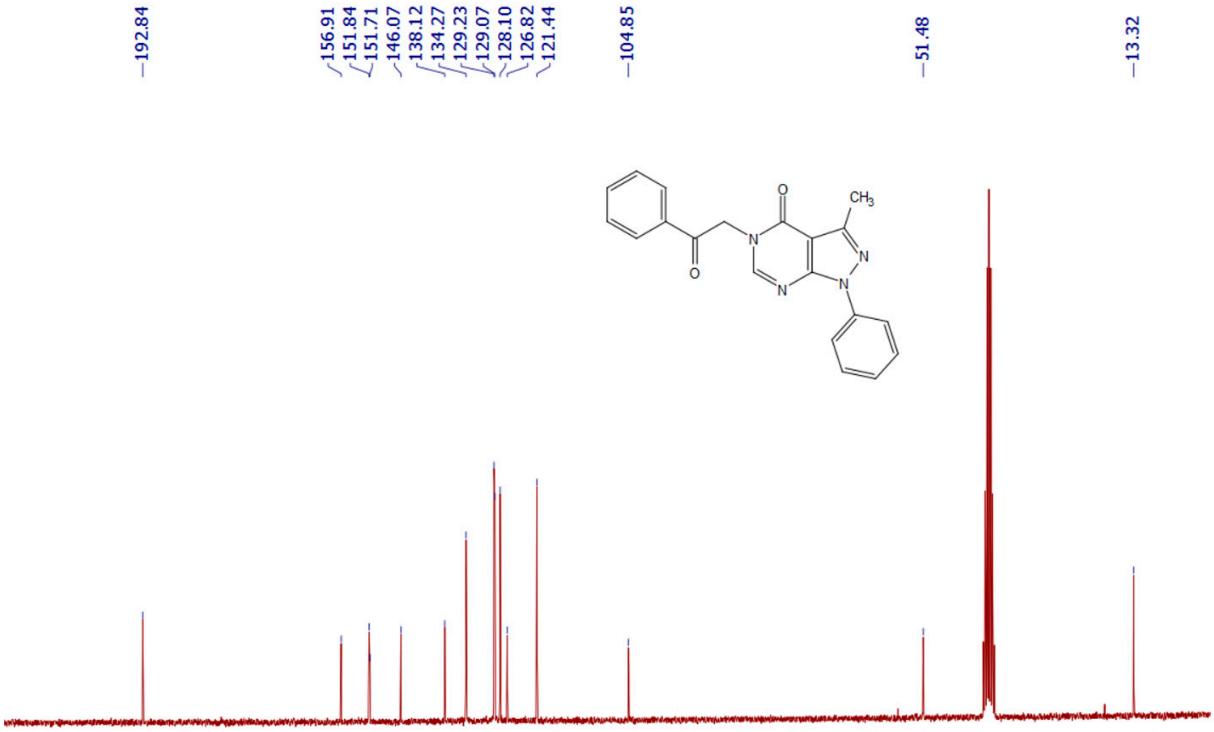
molecules

Figure S11
^{1}H NMR spectrum of compound **P4**.



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Figure S12
^{13}C NMR spectrum of compound **P4**.



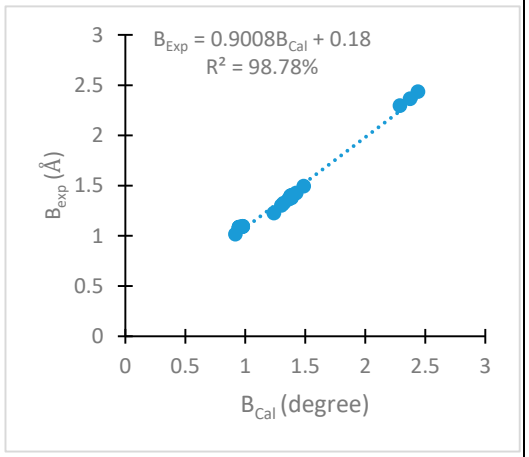
molecules

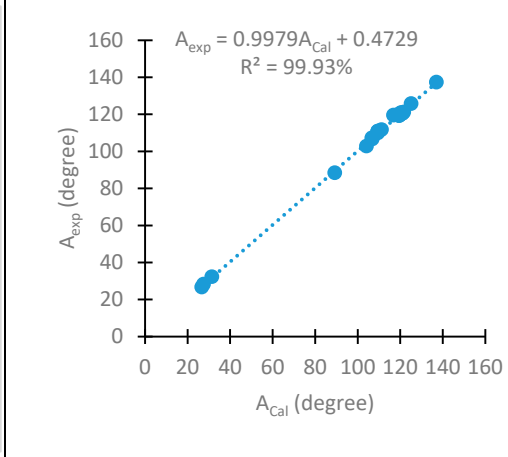
MDPI

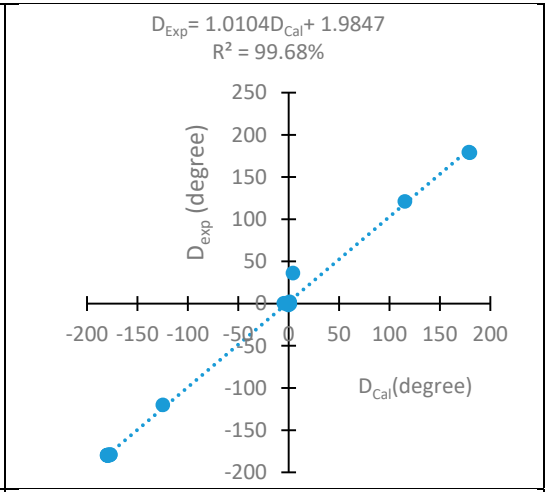
Figure S13

Correlation curves between experimental and calculated bond lengths, bond angles, and dihedral angles of **P1**-**P4**.

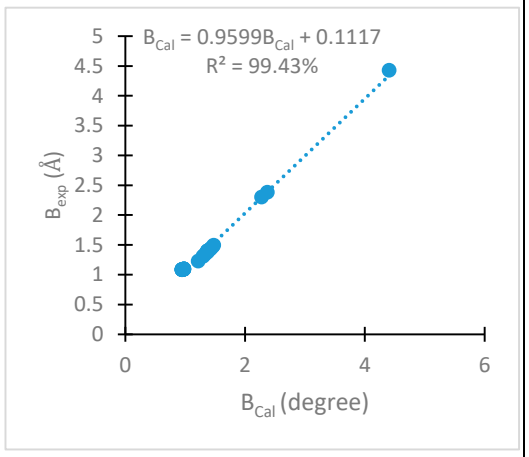
P1

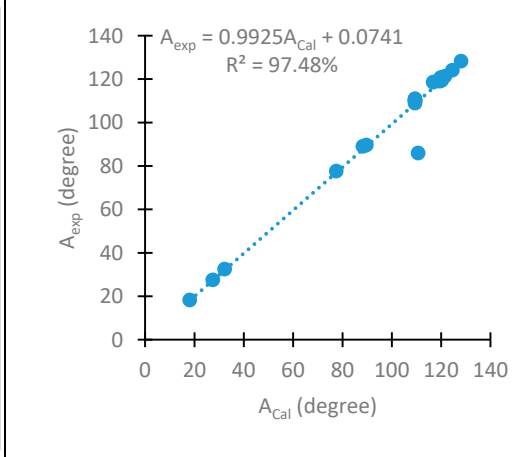


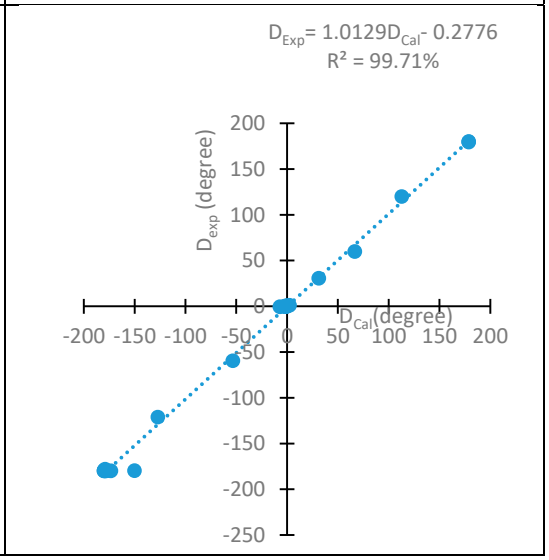




P2

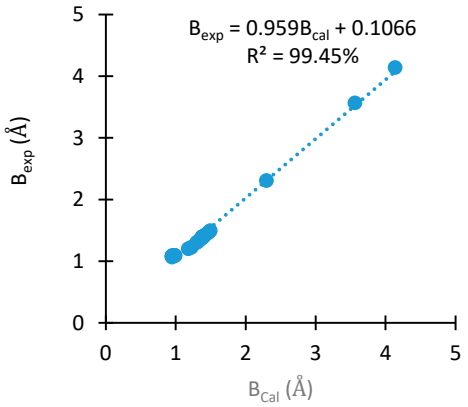


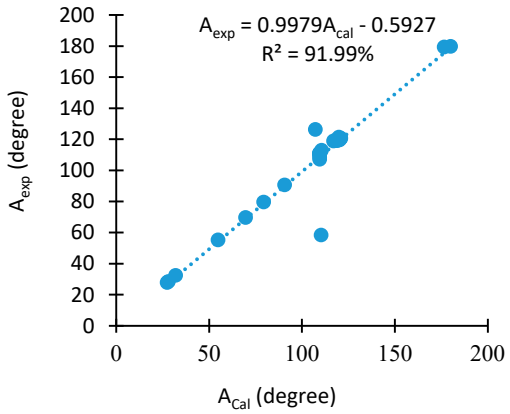


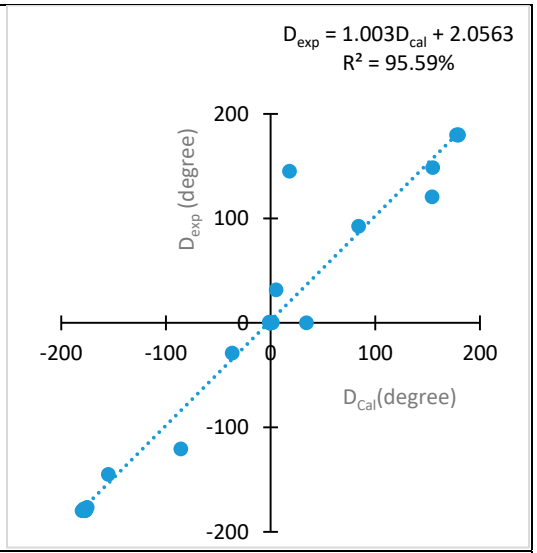


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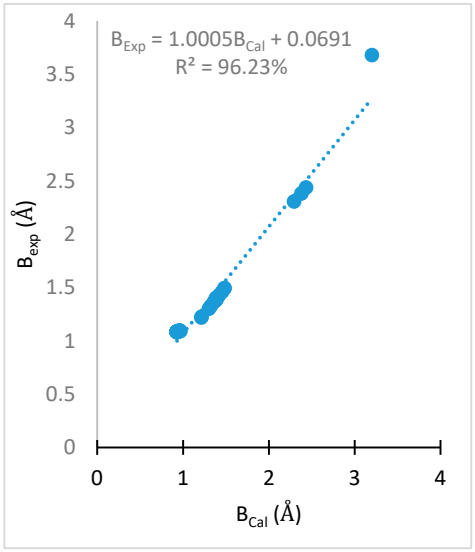
P3

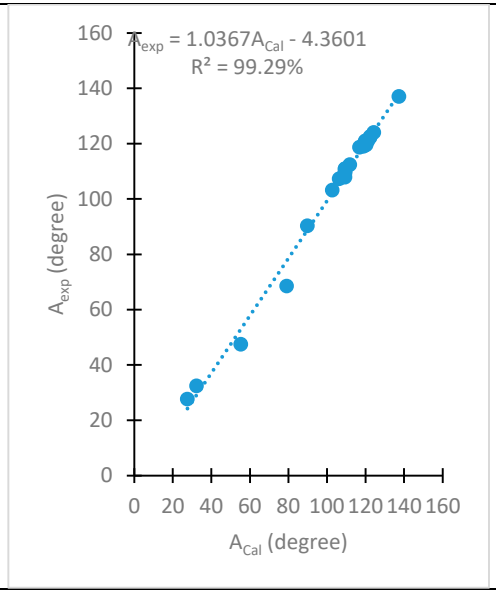


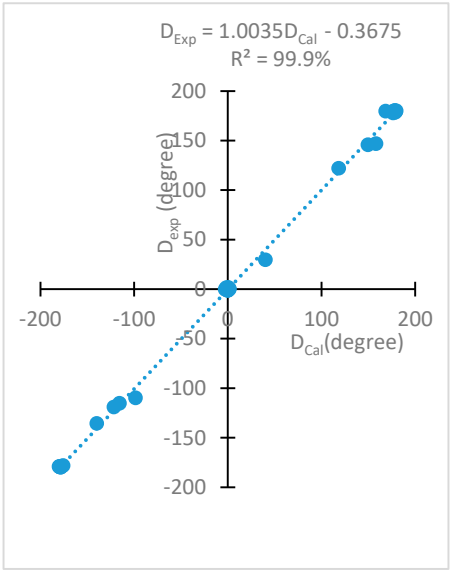




P4







Note: B for bond length, A for bond angle, and D for dihedral angle

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Table S1
The crystal data and structure refinement details of **P1**.

Chemical formula	$C_{12}H_{10}N_4O$
Formula weight	226.24 g/mol
Temperature	171(2) K
Wavelength	0.71073 Å
Crystal size	0.069 x 0.095 x 0.289 mm
Crystal habit	colorless column
Crystal system, Space group	monoclinic, P 1 21/n 1
Cell parameters	a = 5.0757(2) Å
	b = 12.2023(6) Å
	c = 16.9251(8) Å
	α = 90° (2)° β = 95.009(2)° γ = 90° (3)°
Volume	1044.26(8) $Å^3$
Z	4
Density (calculated)	1.439 g/cm^3
Absorption coefficient	0.098 mm^{-1}
F_{000}	472
Index ranges	-7<=h<=7
	-17<=k<=17
	-23<=l<=23
Reflections collected	41497
Independent reflections	3071 [R(int) = 0.0554]
Absorption correction	Numerical
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3071 / 1 / 159
Goodness-of-fit on F^2	1.033
Final [I> 2σ(I)]	R1 = 0.0432, wR_2 = 0.1047
R indices (all data)	R1 = 0.0665, wR_2 = 0.1185
Largest diff. Peak and hole	0.233 and -0.226 $eÅ^{-3}$

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Table S2
The crystal data and structure refinement details of compound **P2**.

Chemical formula	$C_{13}H_{12}N_4O$
Formula weight	240.27 g/mol
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal size	0.118 x 0.263 x 0.328 mm
Crystal habit	colorless plate
Crystal system, Space group	Monoclinic, P 1 21/c 1
Cell parameters	a = 10.551(4) Å
	b = 14.833(6) Å
	c = 7.593(3) Å
	α = 90° β = 101.398(14)° γ = 90°
Volume	1164.9(8) Å^3
Z	4
Density (calculated)	1.370 g/cm^3
Absorption coefficient	0.092 mm^{-1}
F_{000}	504
Index ranges	-17<=h<=17
	-24<=k<=24
	-12<=l<=12
Reflections collected	70045
Independent reflections	5714 [R(int) = 0.0715]
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5714 / 0 / 165
Goodness-of-fit on F^2	1.047
Final [I> 2σ(I)]	R1 = 0.0573, wR_2 = 0.1465
R indices (all data)	R1 = 0.1097, wR_2 = 0.1700
Largest diff. Peak and hole	0.288 and -0.176 eÅ^{-3}

molecules

Table S3
The crystal data and structure refinement details of compound **P3**.

Chemical formula	$C_{15}H_{12}N_4O$
Formula weight	264.29 g/mol
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal size	0.252 x 0.295 x 0.342 mm
Crystal system, Space group	Monoclinic, P 1 21/c 1
Cell parameters	a = 7.2768(4) Å
	b = 16.2369(8) Å
	c = 10.7931(5) Å
	α = 90° β = 91.482(2)° γ = 90°
Volume	1274.81(11) $Å^3$
Z	4
Density (calculated)	1.377 g/cm^3
Absorption coefficient	0.091 mm^{-1}
F_{000}	552
Index ranges	-9<=h<=9
	-21<=k<=21
	-14<=l<=14
Reflections collected	53166
Independent reflections	3199 [R(int) = 0.0412]
Absorption correction	Numerical mu Calculated
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3199 / 0 / 182
Goodness-of-fit on F^2	1.044
Final [$I > 2\sigma(I)$]	R1 = 0.0433, wR_2 = 0.1101
R indices (all data)	R1 = 0.0520, wR_2 = 0.1162
Largest diff. Peak and hole	0.446 and -0.199 $eÅ^{-3}$

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Table S4
The crystal data and structure refinement details of compound **P4**.

Chemical formula	$C_{20}H_{16}N_4O_2$
Formula weight	344.37 g/mol
Temperature	272(2) K
Wavelength	0.71073 Å
Crystal size	0.126 x 0.384 x 0.452 mm
Crystal habit	colorless plate
Crystal system, Space group	Monoclinic, P 1 21/c 1
Cell parameters	a = 13.2177(7) Å
	b = 14.9602(9) Å
	c = 8.5784(5) Å
	α = 90° β = 105.325(2)° γ = 90°
Volume	1635.97(16) Å^3
Z	4
Density (calculated)	1.398 g/cm^3
Absorption coefficient	0.094 mm^{-1}
F_{000}	720
Index ranges	-19<=h<=20
	-23<=k<=23
	-13<=l<=13
Reflections collected	85204
Independent reflections	6209 [R(int) = 0.0402]
Absorption correction	Numerical mu Calculated
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6209 / 0 / 236
Goodness-of-fit on F^2	1.051
Final [I> 2σ(I)]	R1 = 0.0439, wR_2 = 0.1183
R indices (all data)	R1 = 0.0546, wR_2 = 0.1298
Largest diff. Peak and hole	0.420 and -0.294 eÅ^{-3}

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The coordinate and energy information of P1-P4 after optimization

P1; Energy: -757.76 au

Careteisan coordinate:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	6.323995	4.625521	9.042154
2	7	0	5.305075	5.810941	7.363178
3	1	0	5.908924	6.593208	7.586003
4	7	0	3.567456	5.020614	5.973027
5	7	0	2.952357	2.729521	6.516243
6	7	0	3.319418	1.773851	7.435572
7	6	0	5.482316	4.647401	8.153540
8	6	0	4.393648	5.947183	6.358738
9	1	0	4.381901	6.913108	5.865824
10	6	0	3.688397	3.862779	6.682171
11	6	0	4.288105	2.290887	8.173082
12	6	0	4.570786	3.617563	7.741949
13	6	0	1.898603	2.458104	5.596848
14	6	0	1.935109	2.982082	4.302788
15	1	0	2.763189	3.602994	3.992012
16	6	0	0.893791	2.698744	3.421589
17	1	0	0.922913	3.107017	2.417897
18	6	0	-0.168930	1.887776	3.817058
19	1	0	-0.972798	1.666584	3.124635
20	6	0	-0.189304	1.359534	5.107975
21	1	0	-1.010791	0.727346	5.424855
22	6	0	0.837821	1.644702	6.003136
23	1	0	0.829077	1.241958	7.006969
24	6	0	4.929483	1.506915	9.270103
25	1	0	4.481765	0.514614	9.329539
26	1	0	4.805031	2.010749	10.232009
27	1	0	6.003463	1.402803	9.097508

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P2; Energy: -797.07 au

Careteisan coordinate:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	7.464429	5.506600	7.678859
2	7	0	6.248835	7.368683	7.091457
3	7	0	4.027250	3.750958	5.516168
4	7	0	3.547791	5.022373	5.294799
5	7	0	4.210244	7.297297	5.864688
6	6	0	6.473521	5.959969	7.118696
7	6	0	5.432075	5.245085	6.440882
8	6	0	5.154387	3.869621	6.197510
9	6	0	4.378077	5.948829	5.852415
10	6	0	5.160743	7.931774	6.488639
11	1	0	5.108313	9.013264	6.550864
12	6	0	7.247298	8.216094	7.754992
13	1	0	7.316496	7.951746	8.809966
14	1	0	6.946811	9.257164	7.656114
15	1	0	8.223607	8.069967	7.293345
16	6	0	5.948951	2.670053	6.596470
17	1	0	5.451373	1.762292	6.253800
18	1	0	6.065164	2.624512	7.682342
19	1	0	6.953292	2.708638	6.167086
20	6	0	2.315262	5.202831	4.605546
21	6	0	1.323649	4.224979	4.722636
22	1	0	1.504553	3.354249	5.337938
23	6	0	0.120363	4.382027	4.040799
24	1	0	-0.645762	3.620728	4.132753
25	6	0	-0.104034	5.510661	3.252357
26	1	0	-1.043930	5.630869	2.726371
27	6	0	0.890628	6.481250	3.142730
28	1	0	0.729558	7.358303	2.526443
29	6	0	2.104943	6.331539	3.809282
30	1	0	2.877612	7.081144	3.716155

molecules

MDPI

P3; Energy: -873.23 au

Careteisan coordinate:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	4.131853	5.391265	1.288279
2	7	0	4.669722	6.678315	5.184812
3	7	0	3.947050	5.090705	3.568196
4	7	0	5.834446	9.145813	2.886243
5	7	0	5.621541	8.672378	4.160759
6	6	0	5.052860	7.435767	4.121504
7	6	0	4.137826	5.542541	4.845638
8	1	0	3.801327	4.869634	5.627271
9	6	0	4.324625	5.841442	2.409337
10	6	0	4.906505	7.100065	2.772913
11	6	0	5.414432	8.214526	2.046172
12	6	0	3.343752	3.759291	3.358317
13	1	0	2.599910	3.593545	4.140201
14	1	0	2.824511	3.791579	2.400330
15	6	0	4.330689	2.680889	3.356957
16	6	0	5.132639	1.785870	3.362012
17	1	0	5.845161	0.995521	3.361389
18	6	0	5.513580	8.402273	0.568301
19	1	0	5.959056	9.372215	0.345557
20	1	0	4.526324	8.348813	0.102310
21	1	0	6.125683	7.617549	0.116815
22	6	0	5.947721	9.487355	5.282341
23	6	0	5.834772	10.875157	5.166190
24	1	0	5.497301	11.305670	4.233217
25	6	0	6.163590	11.683174	6.250831
26	1	0	6.076271	12.759553	6.157673
27	6	0	6.593659	11.115999	7.450509
28	1	0	6.844563	11.748690	8.293868
29	6	0	6.702276	9.730227	7.556513
30	1	0	7.043313	9.280134	8.481698
31	6	0	6.388813	8.909534	6.475154
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molecules

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P4; Energy: -1141.54 au

Careteisan coordinate:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.401383	4.733593	3.505132
2	8	0	1.925814	7.600187	1.249403
3	7	0	3.591854	6.681797	3.186180
4	7	0	5.822838	6.759508	2.363167
5	7	0	6.733820	4.539478	1.947361
6	7	0	6.309683	3.236515	2.077880
7	6	0	3.451759	5.258748	3.157887
8	6	0	4.731045	7.323955	2.785186
9	1	0	4.695007	8.406419	2.846665
10	6	0	5.750712	5.401891	2.327940
11	6	0	4.653503	4.623417	2.705437
12	6	0	5.065844	3.272047	2.525906
13	6	0	4.292901	2.016976	2.764536
14	1	0	3.398760	1.986185	2.136739
15	1	0	3.959423	1.956378	3.803547
16	1	0	4.913703	1.149308	2.539252
17	6	0	8.061287	4.811345	1.509826
18	6	0	9.082533	3.920092	1.849178
19	1	0	8.850889	3.044768	2.440754
20	6	0	10.381721	4.168310	1.415483
21	1	0	11.171856	3.474517	1.678745
22	6	0	10.669131	5.302543	0.655986
23	1	0	11.682840	5.494059	0.323881
24	6	0	9.643291	6.185900	0.323037
25	1	0	9.854689	7.065360	-0.274248
26	6	0	8.335915	5.943526	0.739171
27	1	0	7.539776	6.623540	0.471585
28	6	0	2.428664	7.465138	3.582201
29	1	0	2.760813	8.369030	4.097766
30	1	0	1.848196	6.868788	4.284904
31	6	0	1.553434	7.853845	2.378676
32	6	0	0.269222	8.560234	2.651041
33	6	0	-0.172125	8.849393	3.950856
34	1	0	0.412158	8.558697	4.814926
35	6	0	-1.378161	9.516409	4.150657
36	1	0	-1.712302	9.734839	5.158043
37	6	0	-2.153916	9.898811	3.057210
38	1	0	-3.093298	10.416408	3.214841
39	6	0	-1.722616	9.614205	1.759423
40	1	0	-2.326198	9.910553	0.909465
41	6	0	-0.519467	8.950320	1.557536
42	1	0	-0.172384	8.722967	0.557438