DFT study of azo linkage effect on homoaromatization of some 1,4-dihydropryridines

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ARTICLE INFO

ABSTRACT

1,4-dihydropryridine derivatives revealed various biological activities and pharmacological properties such as antiviral, antibacterial and anti-inflammatory activities. In this research, density functional theory (DFT) calculations at the B3LYP level are used to optimize the geometry of the compounds. In this study, we were interested in evaluation of homoaromaticity of the selected compounds using nucleus independent chemical shifts NICS(0), NICS(0.5), NICS(1), NICS(1.5) and NICS(2), bond lengths, bond angles and HOMO-LUMO gap.

1. Introduction

1,4-dihydropryridines (DHP's) and their derivatives, have shown several biological and pharmacological properties, such as anti-analgesic, anti-tubercular, anti-tumor, anti-inflammatory, hepatoprotective, cardiovascular disease, geroprotective and stress protective activities [1-4].

Computational chemistry is an important part of chemistry which studies the properties of compounds, their reactions and optimization of existing chemical methods by using advanced and specialized soft wares. One the important areas of study is to analyze that the compounds are aromatic or homoaromatic which this is done through theoretical methods. The index of nuclear independent chemical shift (NICS) is one the most famous criteria which for the first time was proposed by Schleyer et al. in 1996, and received attention from many chemists [5]. By this method we can measure magnetic flux in hypothetical points in the center of molecule and at different distances from it, in a way that at the distance 1 $^\circ A$ upper than the middle of the ring, the effects of σ bond decreases in the molecule and by this method we can better analyze the effects of π

unstable electrons under field effect. This criterion has been used for justifying aromatic property of many systems [6-13].

Homoaromatic compounds are named according to the number of saturated linkages they contain mono for one interruption etc. such as cycloheptatriene, [14] and dihydro-1,2,4,5 tetrazine, [15] Three types of homoaromatic interactions exist: through-bond, through-space, and transannular. The best established homoaromatic molecules are cationic in nature, and only recently have anionic counterparts been identified as homoaromatic. A truly neutral homoaromatic structure has eluded researchers thus far. The focus of this report will be to review recent efforts towards the synthesis and characterization of neutral and anionic homoaromatic compounds [13, 14].

2. Results and Discussion

The main purpose of this research is to calculate density functional theory (DFT) at level B3LYP of those 1,4-dihydropryridine compounds which have aryl azo bridge in order to study the effects of these bridges on the extent of homoaromatic property of these compounds. For this reason, first, all these structures

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(Figure 1) have been optimized by using Gaussian 2009 software (Table 1) and subsequently bonds' length and also some of the bond angles (Table 2), the index of nuclear independent chemical shift (NICS) (Table 3) and calculation of HOMO-LUMO gap (Table 4) in referred compounds were evaluated.

All theoretical calculations were performed using Gaussian 09W program package 18 without any constraint on the geometry. 46 possible structures of azo linked heterocycles were fully optimized at the B3LYP level, using 6-311G^{++}(d) basis set.

R= H, CH$_3$, OCH$_3$, NH$_2$, NO$_2$, Cl
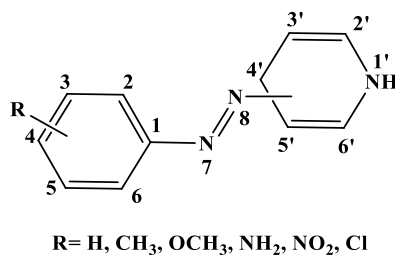
**Figure 1.** Formula of azo-linked azo-linked 1,4-dihydropryridines **1-46**

In view of this and in continuation of our efforts for the preparation and theoretical study of azo linked heterocyclic compounds [16-20] we would like to study a number of 1,4-dihydropryridine structures with different aryl azo linkage. The basis of selecting this series of compounds to study is to analyze existence of homoaromatic property in these compounds from following overall perspective:

i. Comparing bond's length and bond's angel in compounds
ii. Comparing NICS data of the compounds which is related to study five features of these compounds and their classification:

1. Comparing magnetic behavior of some compounds in terms of 1,4-dihydropryridine 's connection point
2. Comparing magnetic behavior of some compounds in terms of the type of phenyl substituent
3. Comparing magnetic behavior of some compounds in terms of the position and frequency of phenyl substituents
4. Comparing magnetic behavior of some compounds in terms of heteroatom

iii. Comparing data resulting from the calculation of HOMO-LUMO gap of compounds

2.1.1. Results of comparing magnetic behavior of some compounds in terms of 1,4-dihydropryridine 's connection point

First, the effect of substituents such as methoxy which is resonating electron donors and also have the effects of

electron withdrawing field was analyzed in various positions of 1,4-dihydropryridine compounds.
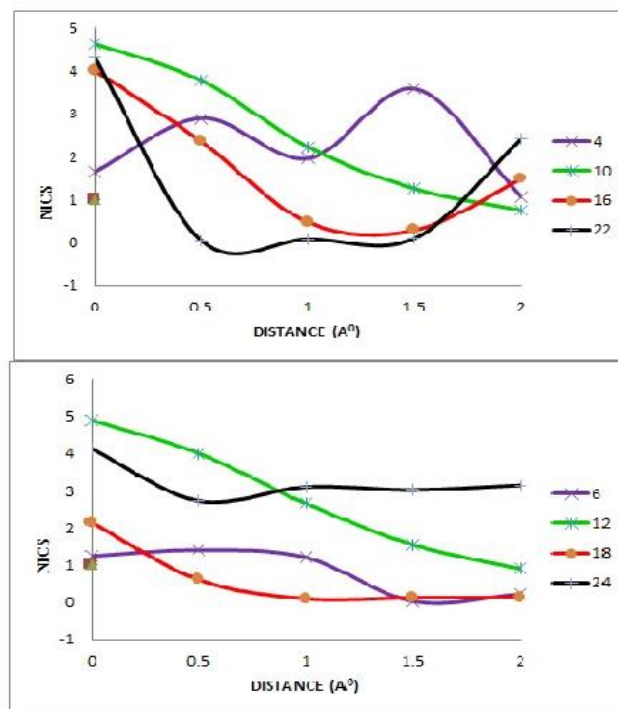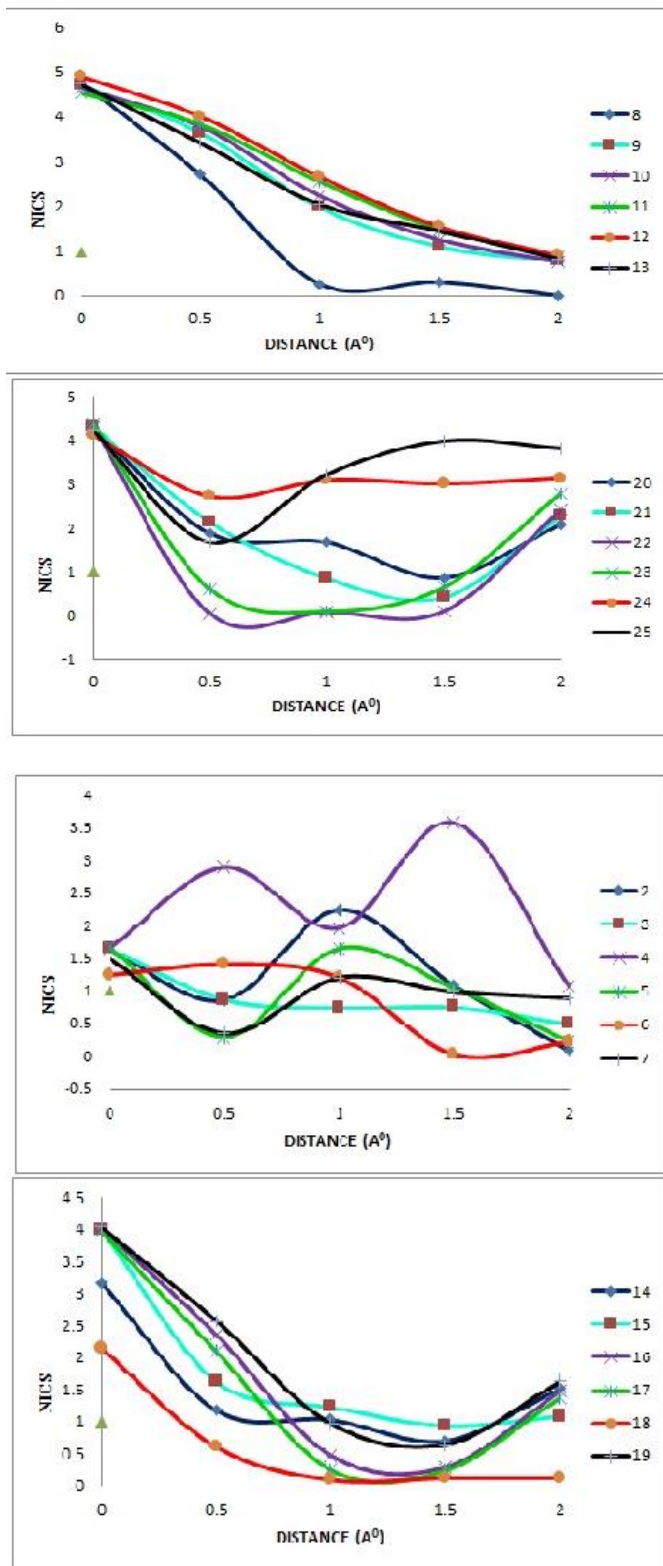

Figure 2. Diagram of comparing magnetic behavior of some compounds in terms of 1,4-dihydropryridine 's connection point

The results of Figure 2 indicate that aryl azo substituents with methoxy group, have close values of NICS at positions 2′ and 3′ of 1,4-dihydropryridine ring, and show little fluctuation in NICS's values by the change of the distance of virtual atom from molecule. In contrast, the position 4′ of 1,4-dihydropryridine has the best values of NICS and with respect to the fact that this position have electron donor resonant effect of this group will result in higher tendency of lone electron pair of 1,4-dihydropryridine's nitrogen for participating in resonance and enhancing its homoaromatic effects. It seems that the existence of broken resonance at positions 2′ or 3′ of 1,4-dihydropryridine reduces the participation of lone electron pair of 1,4-dihydropryridine ring's nitrogen for enhancing homoaromatic effect.

The results in Figure 2 indicate that arylazo substituents with nitro group, have close values of NICS at positions 2′ or 1′ of 1,4-dihydropryridine ring and their fluctuation is low. In contrast, the position 3′ of 1,4-dihydropryridine has lower values of NICS and with respect to the fact that this position doesn't have resonant effects, it acts similar to amino and methoxy groups and the effects of electron withdrawing field of these groups will result in their higher tendency for being homoaromatic effects.

*2.1.2. Results of comparing magnetic behavior of some compounds in terms of the type of phenyl substituent*

with 4-NO$_2$-arylazo linkage **12** is better than 4-CH$_3$O-arylazo-1,4-dihydropryridine **10** (Figure 3).

2.2. Comparison of magnetic behavior of some compounds in terms of the position and frequency of phenyl substituents

In this section of research, the values of NICS in 1,4-dihydropryridines, which have aryls with resonant electron donor and electron withdrawing substituent, were studied at various positions of heterocycle ring which the results are as following.

2.2.1 The analysis of the position and frequency on the 4'-aryl substituents of relevant 1,4-dihydropryridines

The analysis of the position and number of nitro substituent (which is a strong resonant and inductive electron withdrawing group) at position 4' of 1,4-dihydropryridine indicates that by the increase of the number of nitro group or its more closeness to 1,4-dihydropryridine ring, the values of NICS decrease. In general, the closeness of the position and the number of studied substituents at position 4' of 1,4-dihydropryridine ring indicate that by increase in the number of groups or their more closeness to 1,4-dihydropryridine ring, the electron density of 1,4-dihydropryridine ring will decrease strongly and therefore, NICS's values will reduce (Figure 4). The analysis of the position and number of amino substituent on aryl ring at position 4' of 1,4-dihydropryridine indicates that by increase in the number of amino group or its more closeness to 1,4-dihydropryridine ring, NICS's values show lower change.
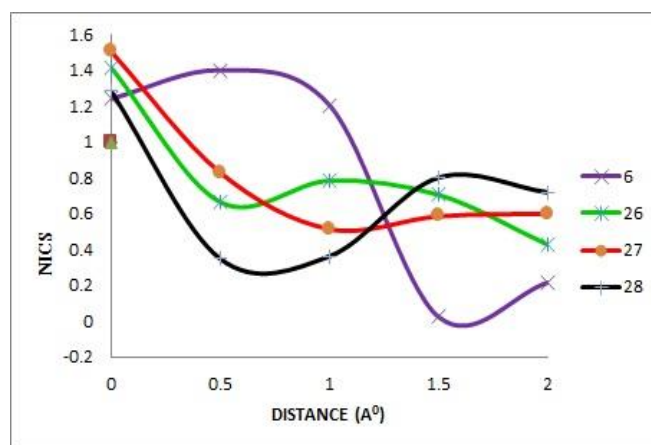
Figure 4. Diagram of the position and frequency on the 4'-aryl substituents of relevant 1,4-dihydropryridines

2.2.2. The analysis of the position and frequency on the 3'-aryl and 2'-aryl substituents of 1,4-dihydropryridines

The analysis of the number or its closeness of electron donor or electron acceptor substituents to heterocycle on aryl ring at positions 3' or 2' of 1,4-

Figure 3. Diagram of comparing magnetic behavior of some compounds in terms of the type of phenyl substituent

The analysis of the substituent effects on different positions of 1,4-dihydropryridines show that electron withdrawing substituents of aryl groups at positions 1', 2' and 4' of 1,4-dihydropryridine rings have relatively better values of NICS, but the type of substituent at positions 3', does not have significant effect on values of NICS. For example, NICS index in 1,4-dihydropryridine

dihydropryridine shows that NICS's values show sensitiveness strangely.

2.2.3. The analysis of the position and frequency on the 1′-aryl substituents of 1,4-dihydropryridines

Existence of electron withdrawing substituent at position 1′, almost do not effective in NICS's values of 1,4-dihydropyridine ring indicates that by more closeness of substituent to 1,4-dihydropyridine ring (*ortho* or *meta* position), but addition number or closeness of amino group at this position caused that NICS's values were increased in NICS(1) characteristically and decreased possibility of resonance consequent of homoaromatic effect (Figure 5).
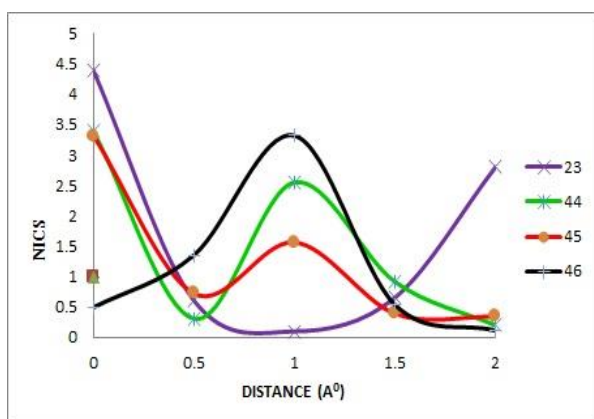
Figure 5. Diagram of the position and frequency on the 1′-aryl substituents of 1,4-dihydropryridines

2.3. Results of comparing magnetic behavior of some compounds in terms of the type of connective bridge
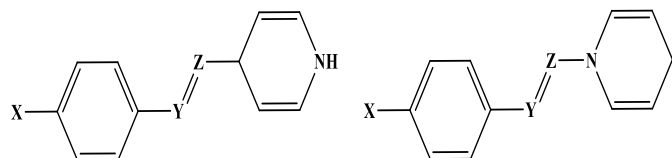
47: X= NO$_2$; Y= N; Z= C
48: X= NO$_2$; Y= C; Z= N
49: X= NO$_2$; Y= C; Z= C
50: X= NH$_2$; Y= N; Z= C
51: X= NH$_2$; Y= C; Z= N
52: X= NH$_2$; Y= C; Z= C

53: X= NO$_2$; Y= N; Z= C
54: X= NO$_2$; Y= C; Z= N
55: X= NO$_2$; Y= C; Z= C
56: X= NH$_2$; Y= N; Z= C
57: X= NH$_2$; Y= C; Z= N
58: X= NH$_2$; Y= C; Z= C
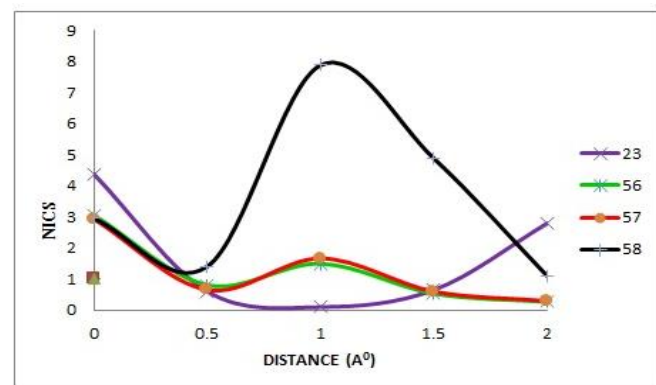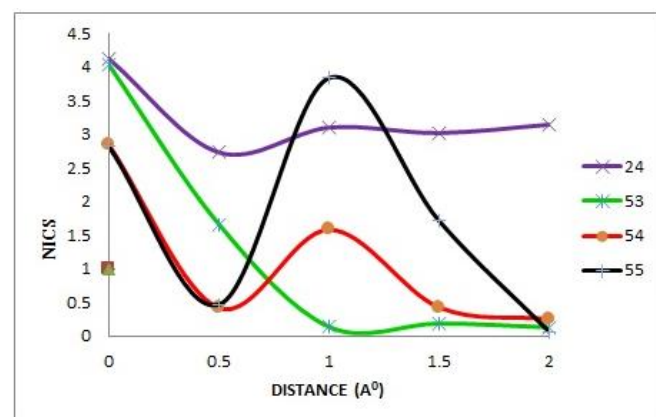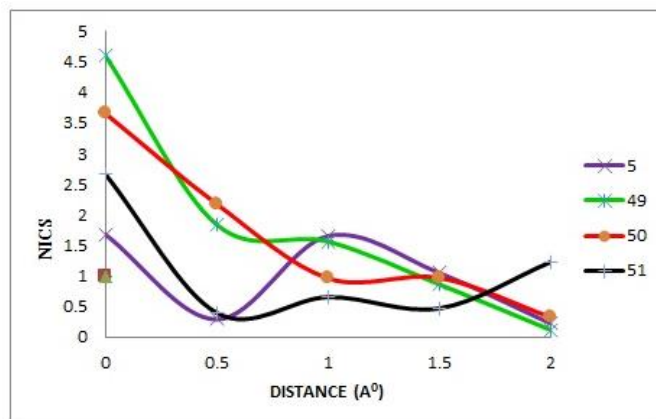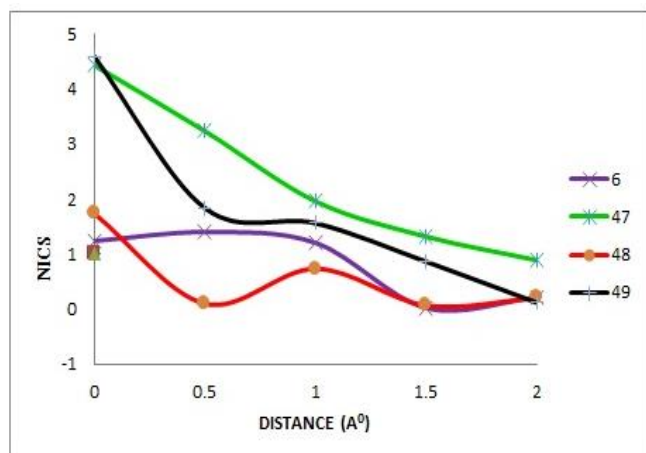
Figure 6. Diagram of comparing magnetic behavior of some compounds in terms of the type of connective bridge

The analysis of some types of 4′-bridges (azo, imine and vinyl) 1,4-dihydropryridine (Figure 6) with electron withdrawing or electron donor substituents indicate that the type of the studied bridges does not have significant effect on NICS's values and the trends due to these bridges are almost the same (Figure 6).

The analysis of type of bridges 1′-linked 1,4-dihydropryridines consist of vinyl-type bridge which have electron withdrawing or electron donor substituent signs that positive NICS(1)'s values that show azo-type linkage is better. In general, the values of NICS which are due to compounds with azo bridge, are better than other bridges. This can be because of relative shortness of these bridges and more effective field effects due to it (Figure 6).

3. Method of analysis

All theoretical calculations were performed using Gaussian 09W program package [18] without any constraint on the geometry. 46 possible structures of azo linked heterocycles were fully optimized at the B3LYP level, using 6-311G^{++}(d) basis set.

Table 1. Calculated total energy of azo-linked 1,4-dihydropryridine

Compound	R	Azo linked site	Total Energy (Ha/particle)
1	-	-	-248.091984197
2	H	4´	-590.092795431
3	4-CH₃	4´	-629.418426397
4	4-CH₃O	4´	-704.644907374
5	4-NH₂	4´	-645.463269763
6	4-NO₂	4´	-794.650661645
7	4-Cl	4´	-1049.71658924
8	H	3´	-590.112402294
9	4-CH₃	3´	-629.437795228
10	4-CH₃O	3´	-704.663919228
11	4-NH₂	3´	-645.480702098
12	4-NO₂	3´	-794.673070597
13	4-Cl	3´	-1049.73684615
14	H	2´	-590.098889718
15	4-CH₃	2´	-629.424841953
16	4-CH₃O	2´	-704.651741429
17	4-NH₂	2´	-645.470924117
18	4-NO₂	2´	-794.655637658
19	4-Cl	2´	-1049.72223900
20	H	1´	-590.090863801
21	4-CH₃	1´	-629.416239070
22	4-CH₃O	1´	-704.642069477
23	4-NH₂	1´	-645.458814118
24	4-NO₂	1´	-794.650694721
25	4-Cl	1´	-1049.71470701
26	3-NO₂	4´	-794.650231401
27	2-NO₂	4´	-794.637894935
28	2,4,6-(NO₂)₃	4´	-1203.73197003
29	3-NO₂	3´	-790.072022069
30	2-NO₂	3´	-790.055687646
31	2,4,6-(NO₂)₃	3´	-1196.72263112
32	3-NO₂	2´	-790.064830953
33	2-NO₂	2´	-790.047485786
34	2,4,6-(NO₂)₃	2´	-1196.70886068
35	3-NO₂	1´	-790.046508977
36	2-NO₂	1´	-790.031223878
37	2,4,6-(NO₂)₃	1´	-1196.69470035
38	3-NH₂	3´	-641.776711066
39	2-NH₂	3´	-641.788949565
40	2,4,6-(NH₂)₃	3´	-751.896736961
41	3-NH₂	2´	-641.774008705
42	2-NH₂	2´	-641.743295893
43	2,4,6-(NH₂)₃	2´	-751.896312964
44	3-NH₂	1´	-641.753504084
45	2-NH₂	1´	-641.761911173
46	2,4,6-(NH₂)₃	1´	-751.866969674

Table 2. Some of calculated bond lengths (A°) and bond angles (°) of azo-linked 1,4-dihydropryridines

Compound	N-C₂'	N-C₆'	N-N	C₂'-N-C₆'	C₃'-C₄'-C₅'
1	1.3982	1.3982	-	118.8474	110.3517
2	1.3852	1.3878	1.2389	118.6732	110.6133
3	1.3855	1.3881	1.2396	118.6342	110.5873
4	1.3858	1.3884	1.2405	118.6044	110.5336
5	1.3863	1.3887	1.2419	118.5647	110.4908
6	1.3867	1.3835	1.2389	118.8119	110.6860
7	1.3874	1.3848	1.2391	118.7114	110.6400
8	1.3635	1.3991	1.2705	120.1809	110.8392
9	1.3644	1.3986	1.2706	120.1562	110.8419
10	1.3659	1.3979	1.2707	120.1312	110.8661
11	1.3687	1.3963	1.2715	120.0573	110.8815
12	1.357	1.4020	1.2754	120.4524	110.9322
13	1.3618	1.3998	1.2717	120.2507	110.8584
14	1.3967	1.3933	1.2521	118.0001	110.3539
15	1.3973	1.3933	1.253	117.9798	110.3524
16	1.3979	1.3931	1.2543	117.9936	110.3552
17	1.3986	1.3927	1.2562	118.0434	110.3692
18	1.3951	1.3945	1.2534	117.9823	110.3957
19	1.3965	1.3939	1.2529	117.9564	110.3591
20	1.4004	1.4060	1.2579	119.1553	110.9286
21	1.3999	1.4054	1.2577	119.1397	110.8917
22	1.3991	1.4048	1.2571	119.1162	110.8471
23	1.3974	1.4030	1.2565	119.0839	110.7632
24	1.4036	1.4091	1.2638	119.2223	111.1248
25	1.4014	1.4069	1.2596	119.1699	110.9799
26	1.3845	1.3867	1.238	118.7573	110.6999
27	1.3856	1.3872	1.2378	118.7105	110.9318
28	1.3804	1.3819	1.2350	119.3862	111.0691
29	1.3635	1.4120	1.3147	119.9732	110.9151
30	1.3616	1.4131	1.3169	120.0307	110.9075
31	1.3517	1.4187	1.319	120.4997	111.0701
32	1.3817	1.3967	1.3008	119.1877	110.8129
33	1.3814	1.3965	1.3015	119.1687	110.8437
34	1.3768	1.3998	1.3034	119.0859	111.0175
35	1.4075	1.4125	1.3013	119.8622	111.2384
36	1.408	1.4130	1.3036	119.8914	111.2831
37	1.411	1.4184	1.3141	120.2399	111.6471
38	1.3709	1.4089	1.3109	119.7423	110.8988
39	1.3757	1.4058	1.3207	119.7324	110.951
40	1.3849	1.3993	1.3258	119.5982	111.1717
41	1.3832	1.3939	1.2991	119.2576	110.6997
42	1.3908	1.4003	1.2887	118.8737	110.2877
43	1.3891	1.3929	1.3233	119.6718	110.7037
44	1.4031	1.4092	1.2944	119.8065	111.0348
45	1.4009	1.4063	1.2972	119.7562	110.881
46	1.3977	1.3995	1.2985	119.3919	110.5415

Table 3. Calculated NICS indexes of azo-linked 1,4-dihydropryridines

Compound	NICS (0)	NICS (0.5)	NICS (1)	NICS (1.5)	NICS (2)
1	3.8268	2.7990	1.9223	1.5279	0.9884
2	1.6349	0.8553	2.2480	1.0828	0.0884
3	1.6462	0.8636	0.7349	0.7435	0.4959
4	1.6534	2.8952	1.9616	3.5873	1.0774
5	1.6763	0.2921	1.6552	1.0479	0.2244
6	1.2428	1.4021	1.2067	0.0244	0.2167
7	1.5017	0.3468	1.2052	0.9842	0.8877
8	4.7545	2.7049	0.2628	0.3067	0.0071
9	4.7044	3.6394	1.9668	1.0952	0.7765
10	4.6460	3.7842	2.2324	1.2566	0.7630
11	4.5267	3.8298	2.5470	1.4835	0.8696
12	4.8923	4.0078	2.6565	1.5450	0.8978
13	4.7220	3.4163	2.0394	1.4504	0.8300
14	3.1667	1.1800	1.0346	0.7015	1.5178
15	3.9934	1.6292	1.2281	0.9418	1.0877
16	4.0270	2.3601	0.4739	0.2922	1.4775
17	3.9738	2.0983	0.2501	0.2422	1.3751
18	2.1474	0.6068	0.0960	0.1241	0.1274
19	4.0361	2.5778	0.9706	0.6451	1.6276
20	4.3086	1.8864	1.6804	0.8753	2.0951
21	4.3179	2.1409	0.8574	0.4197	2.2862
22	4.3384	0.0481	0.0833	0.1040	2.4179
23	4.3849	0.6071	0.1016	0.6561	2.7991
24	4.1286	2.7342	3.1032	3.0221	3.1462
25	4.2333	1.6795	3.2355	3.9921	3.8275
26	1.4162	0.6659	0.7851	0.7059	0.4274
27	1.5056	0.8299	0.5144	0.5866	0.6016
28	1.2842	0.3491	0.3635	0.8031	0.7198
29	3.5969	2.6792	1.7238	1.3774	0.9487
30	3.5288	2.4697	1.5357	1.3673	0.9633
31	3.5504	2.5623	1.6444	1.3017	0.8625
32	3.8930	2.2446	0.5814	1.1568	1.1077
33	4.4636	2.6266	0.7182	1.0583	0.8513
34	3.9726	2.5684	2.0596	1.7064	1.0830
35	3.3236	1.5781	0.3413	0.6387	0.5802
36	3.1655	1.9241	1.2007	2.1173	0.1358
37	2.8779	0.8284	0.2192	2.1435	0.3226
38	3.4097	2.3147	1.1686	1.0353	0.9120
39	3.0509	1.8306	0.7694	1.0338	0.9396
40	2.5483	1.7309	1.1674	1.2517	0.9423
41	3.7069	2.5022	1.4839	1.1163	0.6930
42	3.1147	2.1764	0.4996	1.3412	0.2852
43	2.9518	1.9826	1.5280	1.4820	1.0806
44	3.3892	0.3098	2.5503	0.9175	0.2015
45	3.3131	0.7248	1.5654	0.3938	0.3420
46	0.4955	1.3539	3.3187	0.5391	0.1145

Table 4. Calculated HOMO-LUMO gap of azo-linked 1,4-dihydropyridines

Compound	HOMO (Ha/particle)	LUMO (Ha/particle)	Gap (kcal.mol^{-1})
1	-0.2804070230	-0.1531491310	79.79
2	-0.2787140570	-0.1958241590	51.97
3	-0.2789330500	-0.1958206200	52.11
4	-0.2789473010	-0.1887834680	56.53
5	-0.2791794640	-0.1896711820	56.12
6	-0.2700374660	-0.1929697160	48.32
7	-0.2784766990	-0.1921590550	54.12
8	-0.2802962110	-0.2016005280	49.34
9	-0.2794520920	-0.1998831070	49.88
10	-0.2759390760	-0.1945201530	51.04
11	-0.2746465710	-0.1939679450	50.58
12	-0.2800793330	-0.2057630170	46.59
13	-0.2781189540	-0.1986601920	49.82
14	-0.2853586550	-0.2063091870	49.56
15	-0.2852098440	-0.2047402840	50.45
16	-0.2845655120	-0.1986564490	53.86
17	-0.2845275800	-0.1990804640	53.57
18	-0.2853195640	-0.2071121870	49.03
19	-0.2849932080	-0.2029776010	51.42
20	-0.2804526070	-0.1855181210	59.52
21	-0.2791091930	-0.1833705390	60.02
22	-0.2737466020	-0.1771093490	60.59
23	-0.2718403000	-0.1763028370	59.90
24	-0.2805910580	-0.1930180090	54.90
25	-0.2771833220	-0.1821040460	59.61
26	-0.2779815420	-0.1941772270	52.54
27	-0.2761892040	-0.1830288440	58.41
28	-0.2900538570	-0.1853086840	46.86
29	-0.2801534390	-0.2016366630	49.23
30	-0.2793959570	-0.2003817200	49.54
31	-0.2795935520	-0.1960635150	52.37
32	-0.2854083080	-0.2080399100	48.50
33	-0.2798148810	-0.2080687310	44.98
34	-0.2828075430	-0.1996266740	52.15
35	-0.2806559460	-0.1865182970	59.02
36	-0.2796884350	-0.1838317280	60.10
37	-0.2813023760	-0.1850934420	60.32
38	-0.2801493760	-0.2007696780	49.77
39	-0.2756867710	-0.1966304540	49.56
40	-0.2685192460	-0.1856208560	51.97
41	-0.2847193440	-0.2065573050	49.00
42	-0.2769730490	-0.1955499510	51.05
43	-0.2807319630	-0.1925581890	55.28
44	-0.2801805160	-0.1845230980	59.97
45	-0.2734027390	-0.1806035210	58.18
46	-0.2632081030	-0.1668298360	60.42

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