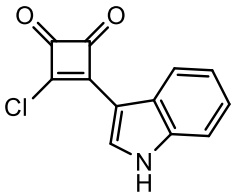
D. H. Lande , A. Nasereddin, A. Alder, T. W. Gilberger, R. Dzikowski, J. Grünefeld, C. Kunick

Synthesis and Antiplasmodial Activity of Bisindolylcyclobutenediones: Supplementary Materials

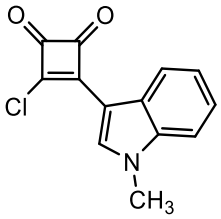
Content: Table S1: Structures of all test compounds 2 (pages 1-5), Table S2: ^{1}H NMR-spectra of test compounds displayed in Table 2 (Pages 6-12), Figure S1: Docking pose of **2b** and **2ad** in a *Pf*GSK-3 homology model (page 13).

Table S1: Structures of compounds mentioned in the article

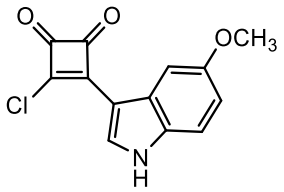
3-Chloro-4-(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(5a)**



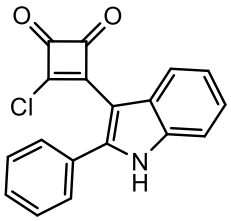
3-Chloro-4-(1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(5b)**



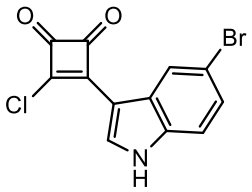
3-Chloro-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(5c)**



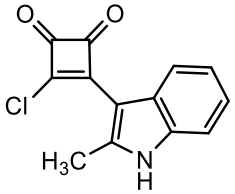
3-Chloro-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(5d)**



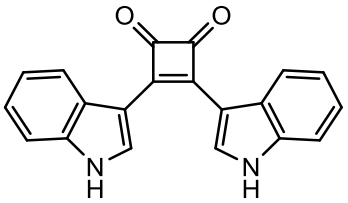
3-(5-Bromo-1H-indol-3-yl)-4-chlorcyclobut-3-ene-1,2-dione **(5e)**



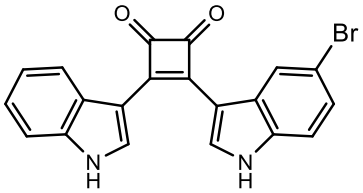
3-Chloro-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(5f)**



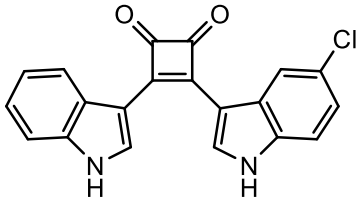
3,4-Bis(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2a)**



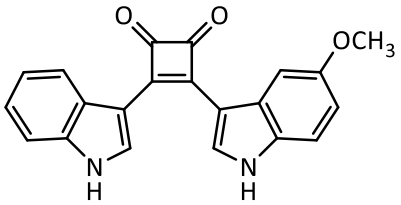
3-(5-Bromo-1H-indol-3-yl)-4-(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2b)**



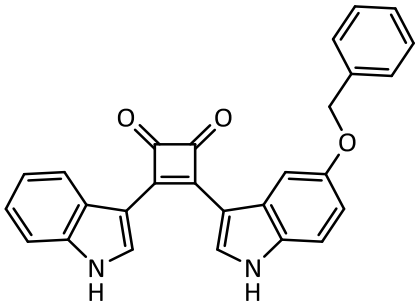
3-(5-Chloro-1H-indol-3-yl)-4-(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2c).**



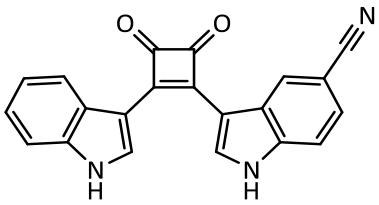
3-(1H-Indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2d)**



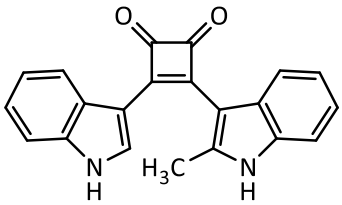
3-[5-(Benzyloxy)-1H-indol-3-yl]-4-(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2e)**



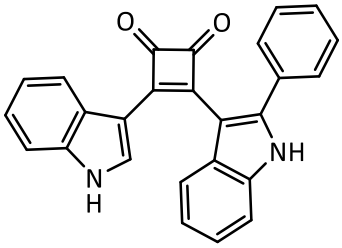
3-[2-(1H-Indol-3-yl)-3,4-dioxocyclobut-1-ene-1-yl]-1H-indol-5-carbonitrile **(2f)**



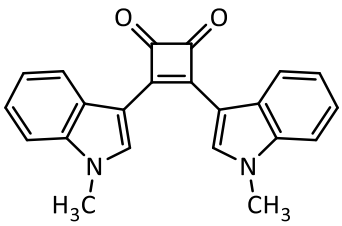
3-(1H-Indol-3-yl)-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2g)**



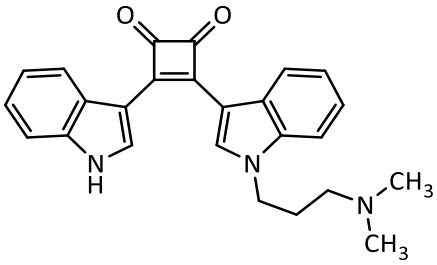
3-(1H-Indol-3-yl)-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2h)**



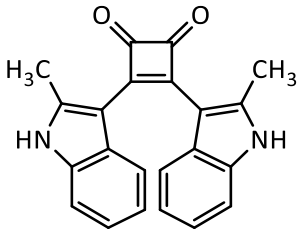
3,4-Bis(1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2i)**



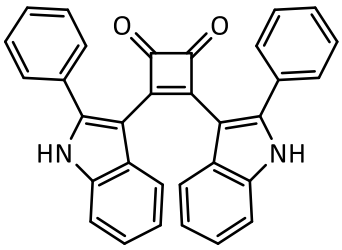
3-{1-[3-(Dimethylamino)propyl]-1H-indol-3-yl}-4-(1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2k)**



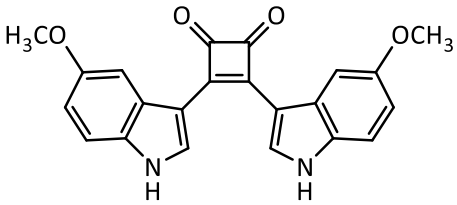
3,4-Bis(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2l).**



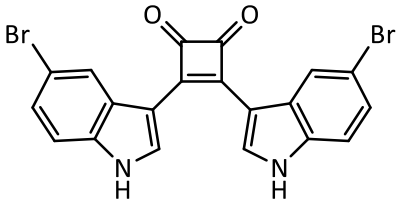
3,4-Bis(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2m)**



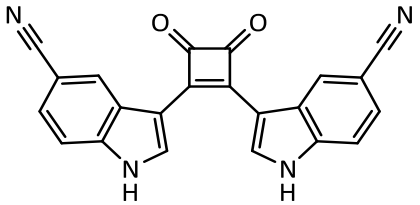
3,4-Bis(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2n)**



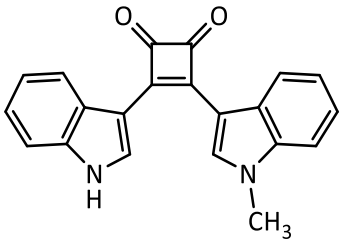
3,4-Bis(5-bromo-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2o)**



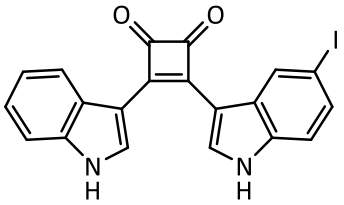
3,3′-(3,4-Dioxocyclobut-1-ene-1,2-diyl)bis(1H-indole-5-carbonitrile) **(2p)**



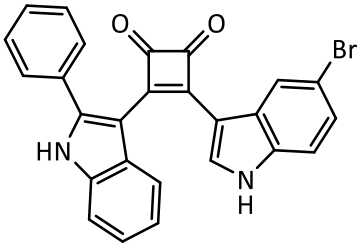
3-(1H-Indol-3-yl)-4-(1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2q)**



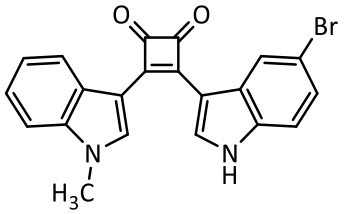
3-(1H-Indol-3-yl)-4-(5-iod-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2r)**



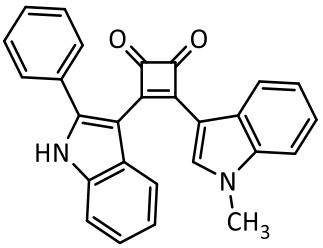
3-(5-Bromo-1H-indol-3-yl)-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2s)**



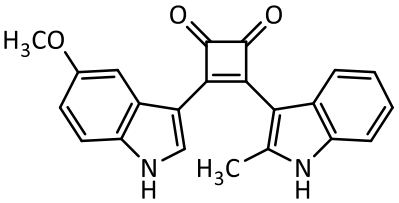
3-(5-Bromo-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2t)**



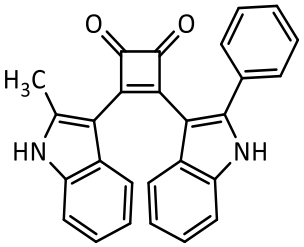
3-(1-Methyl-1H-indol-3-yl)-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2u)**



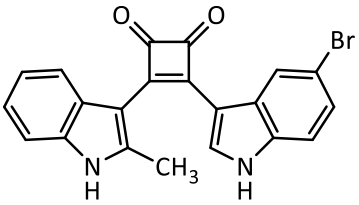
3-(5-Methoxy-1H-indol-3-yl)-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2v)**



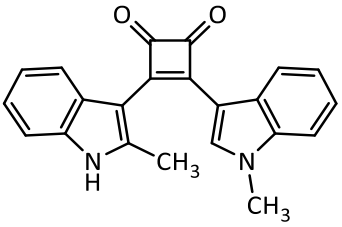
3-(2-Methyl-1H-indol-3-yl)-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2w)**



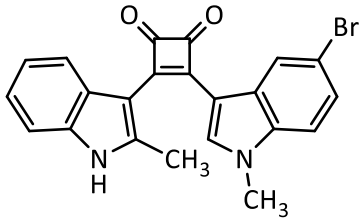
3-(5-Bromo-1H-indol-3-yl)-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2x)**



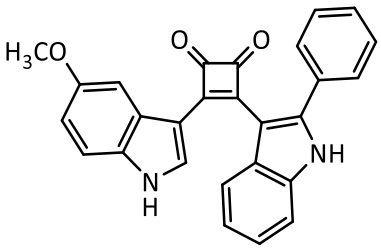
3-(1-Methyl-1H-indol-3-yl)-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2y)**



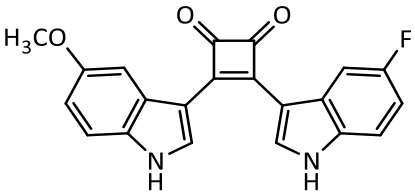
3-(5-Bromo-1-methyl-1H-indol-3-yl)-4-(2-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2z)**



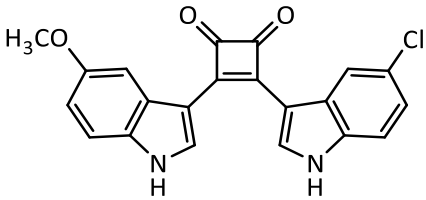
3-(5-Methoxy-1H-indol-3-yl)-4-(2-phenyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2aa)**



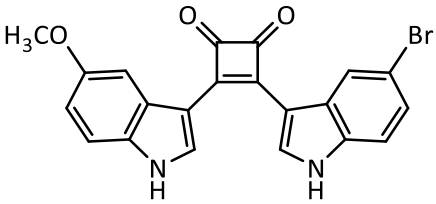
3-(5-Fluoro-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ab)**



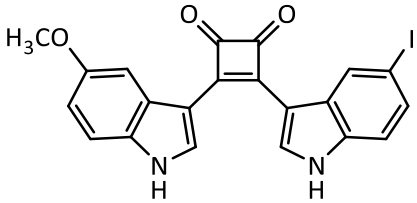
3-(5-Chloro-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ac)**



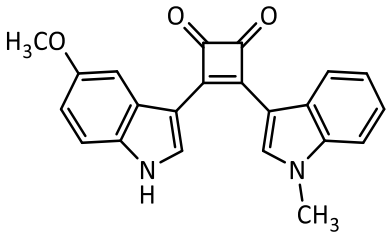
3-(5-Bromo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ad)**



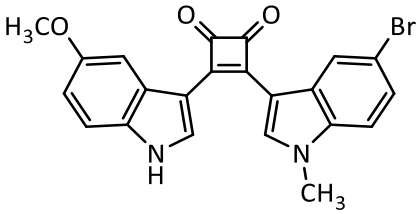
3-(5-Iodo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ae)**



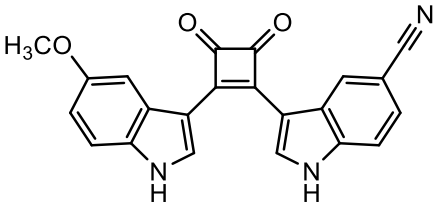
3-(5-Methoxy-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2af)**



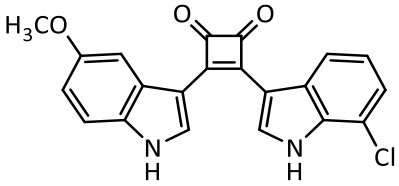
3-(5-Bromo-1-methyl-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ag)**



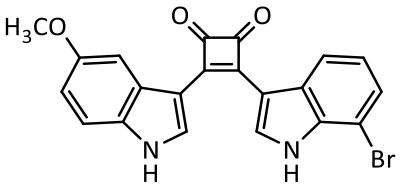
3-[2-(5-Methoxy-1H-indol-3-yl)-3,4-dioxocyclobut-1-en-1-yl]-1H-indole-5-carbonitrile **(2ah)**



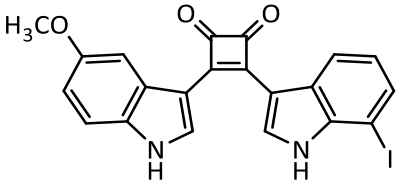
3-(7-Chloro-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ai)**



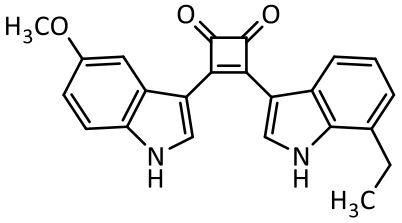
3-(7-Bromo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2aj)**



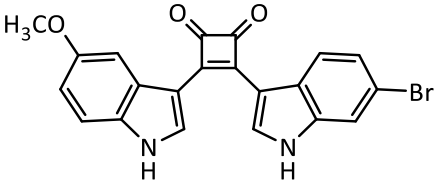
3-(7-Iodo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ak)**



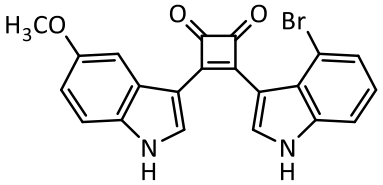
3-(7-Ethyl-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2al)**



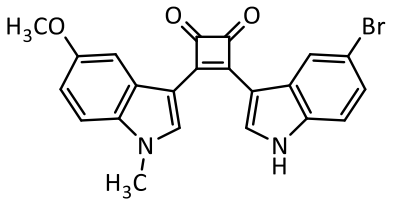
3-(6-Bromo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2am)**



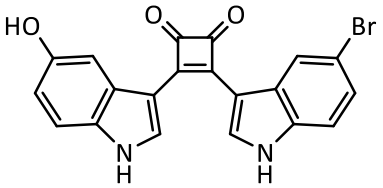
3-(4-Bromo-1H-indol-3-yl)-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2an)**



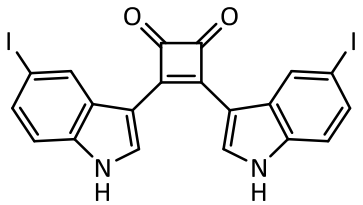
3-(5-Bromo-1H-indol-3-yl)-4-(5-methoxy-1-methyl-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ao)**



3-(5-Bromo-1H-indol-3-yl)-4-(5-hydroxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ap)**



3,4-Bis(5-iodo-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2aq)**



3-[5-(Benzyloxy)-1H-indol-3-yl]-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione **(2ar)**

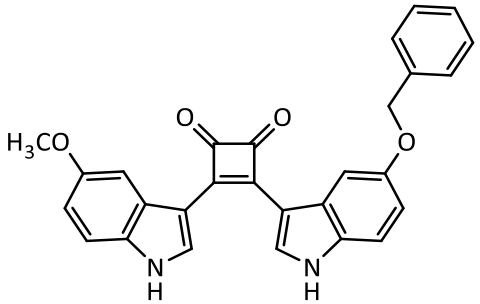
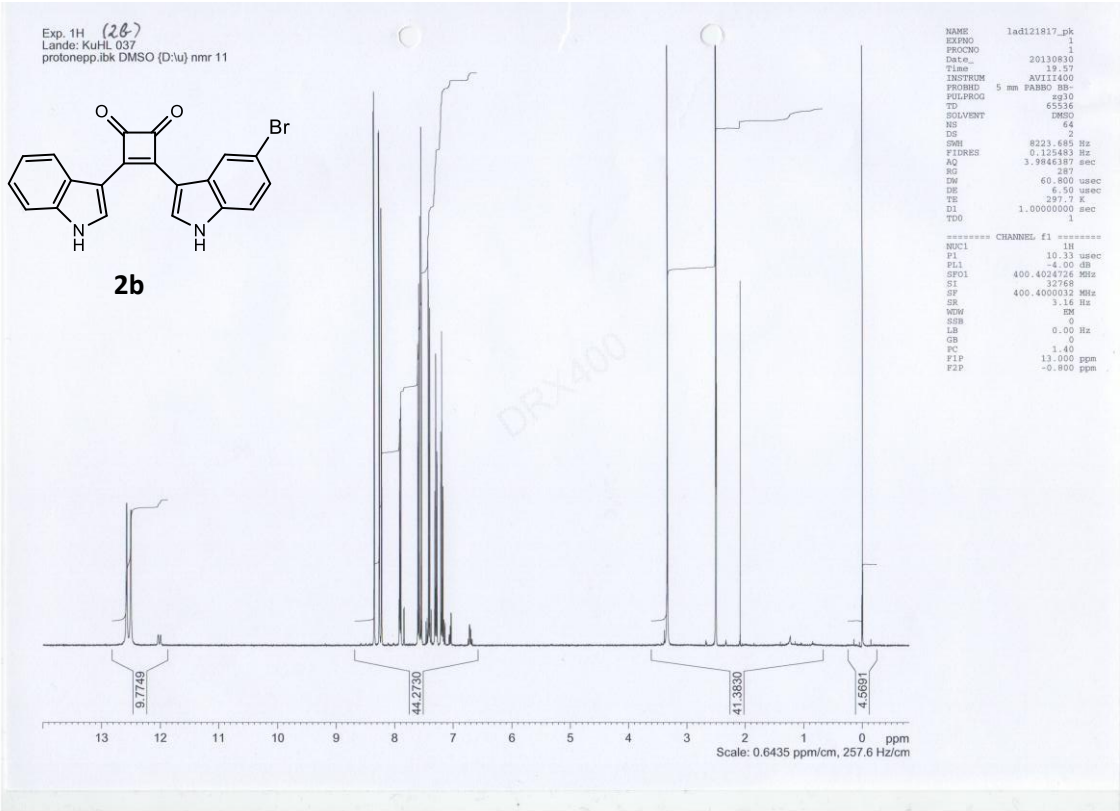
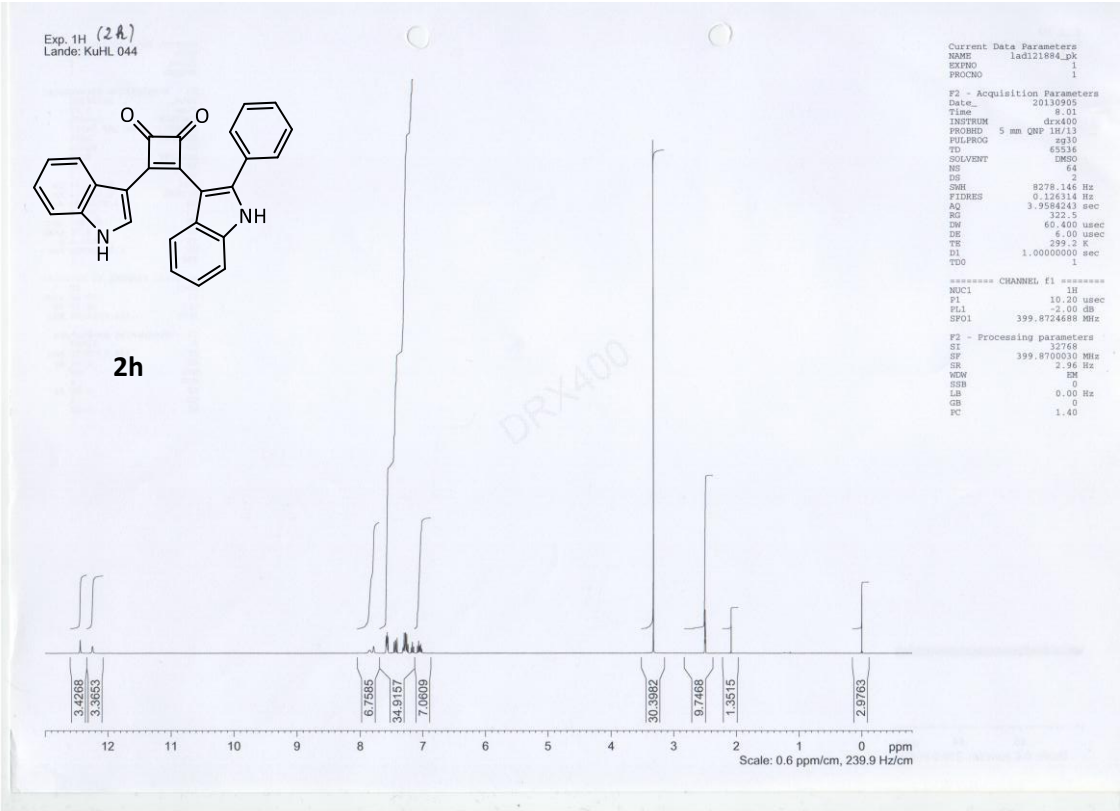
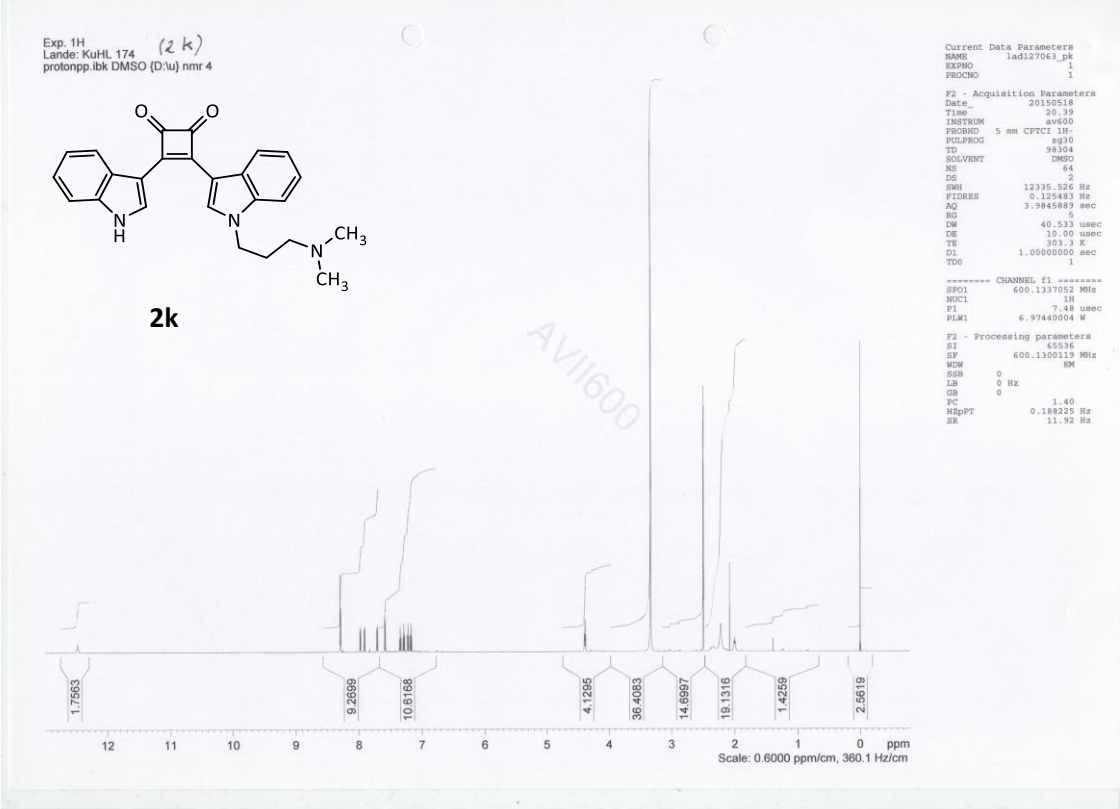
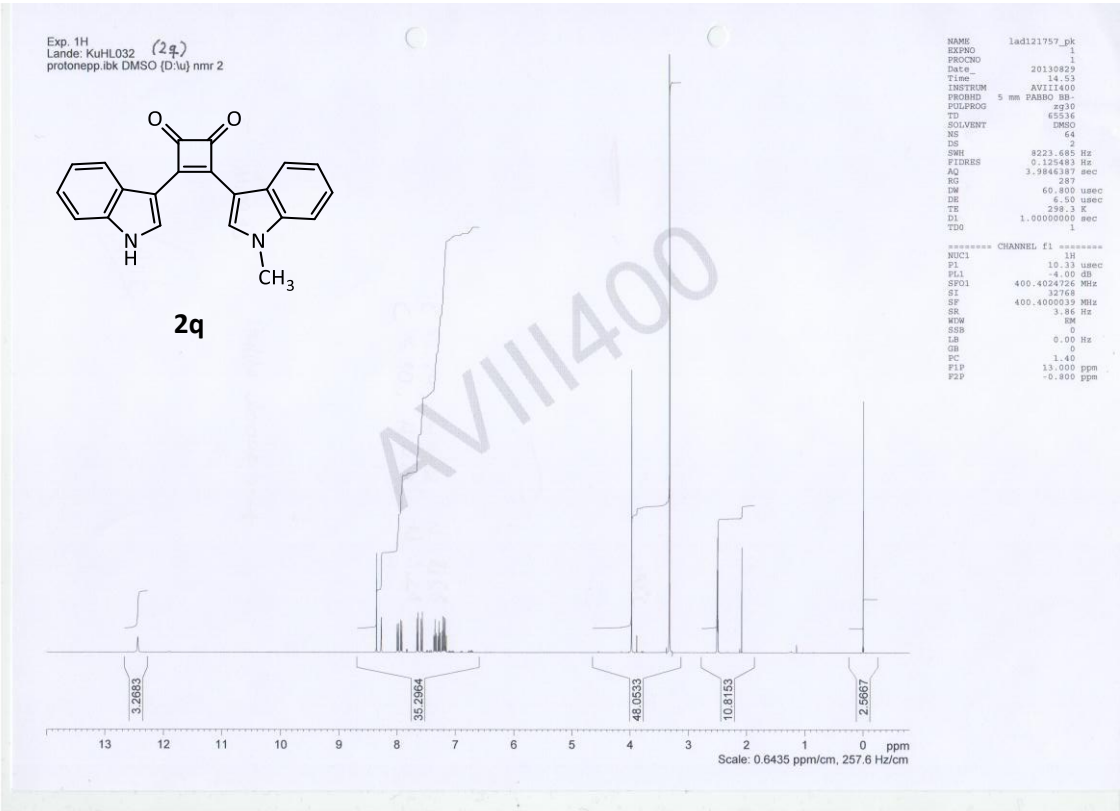


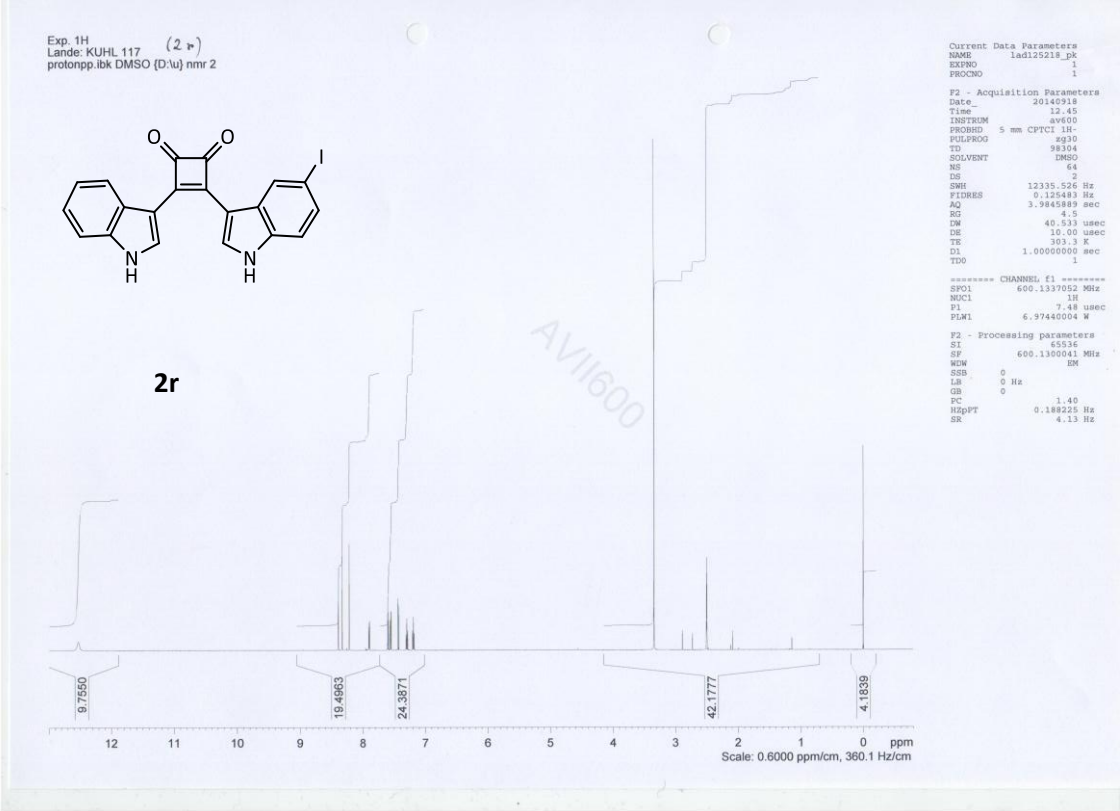
Table S2: ^{1}H NMR Spectra of compounds displayed in Table 2

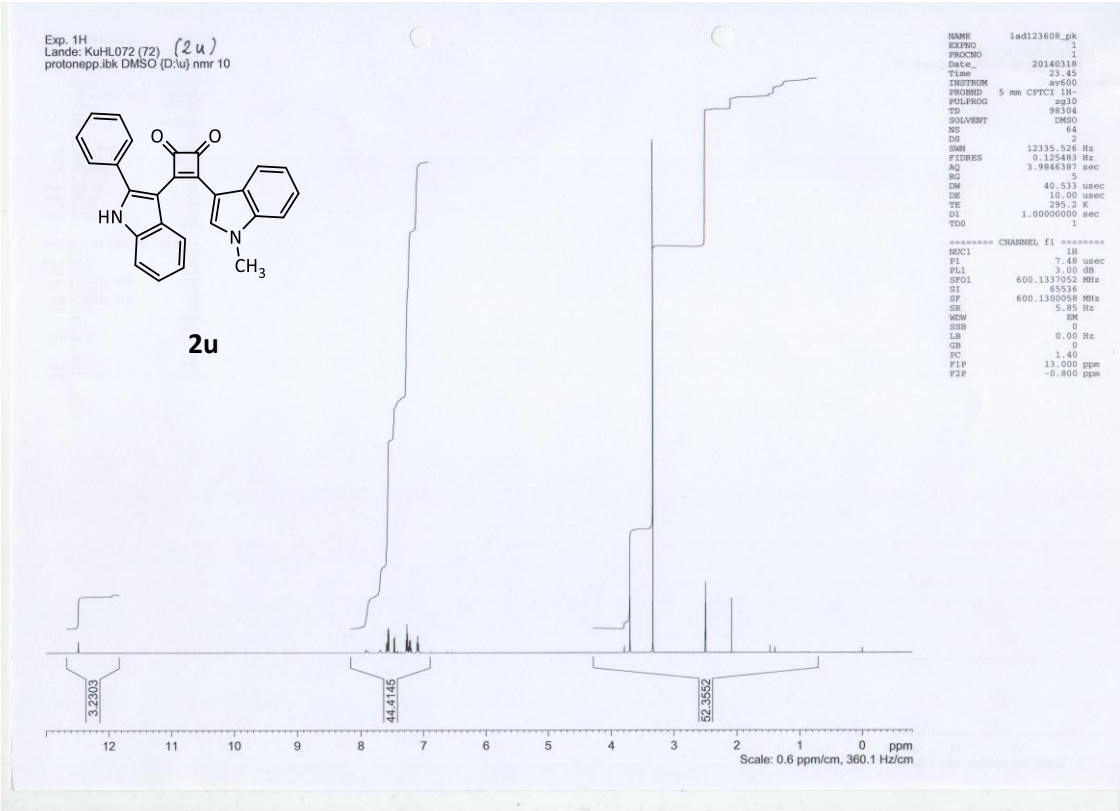


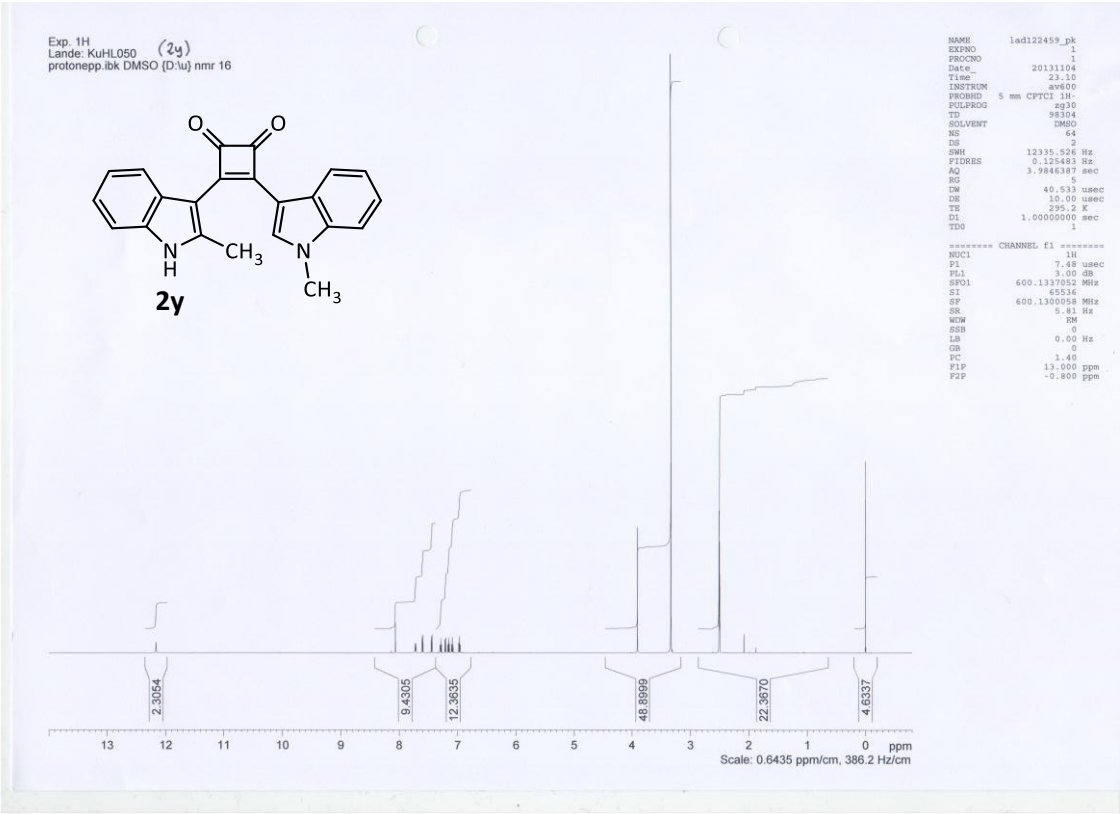


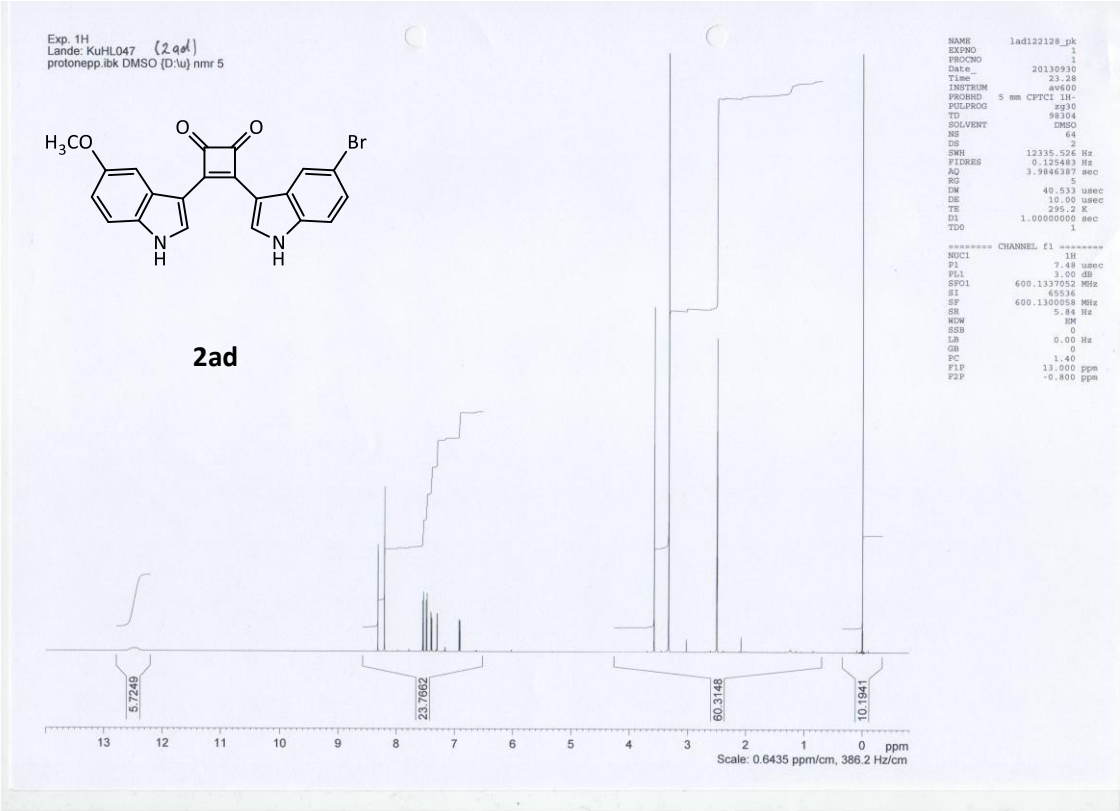

Exp. 1H
Lande: KuHL 174 (2k)
protonpp.ibk DMSO {D:\u} nmr 4
2k
AVII600
1.7563
9.2699
10.6168
4.1295
36.4083
14.6997
19.1316
1.4259
2.5619
ppm
Scale: 0.6000 ppm/cm, 360.1 Hz/cm

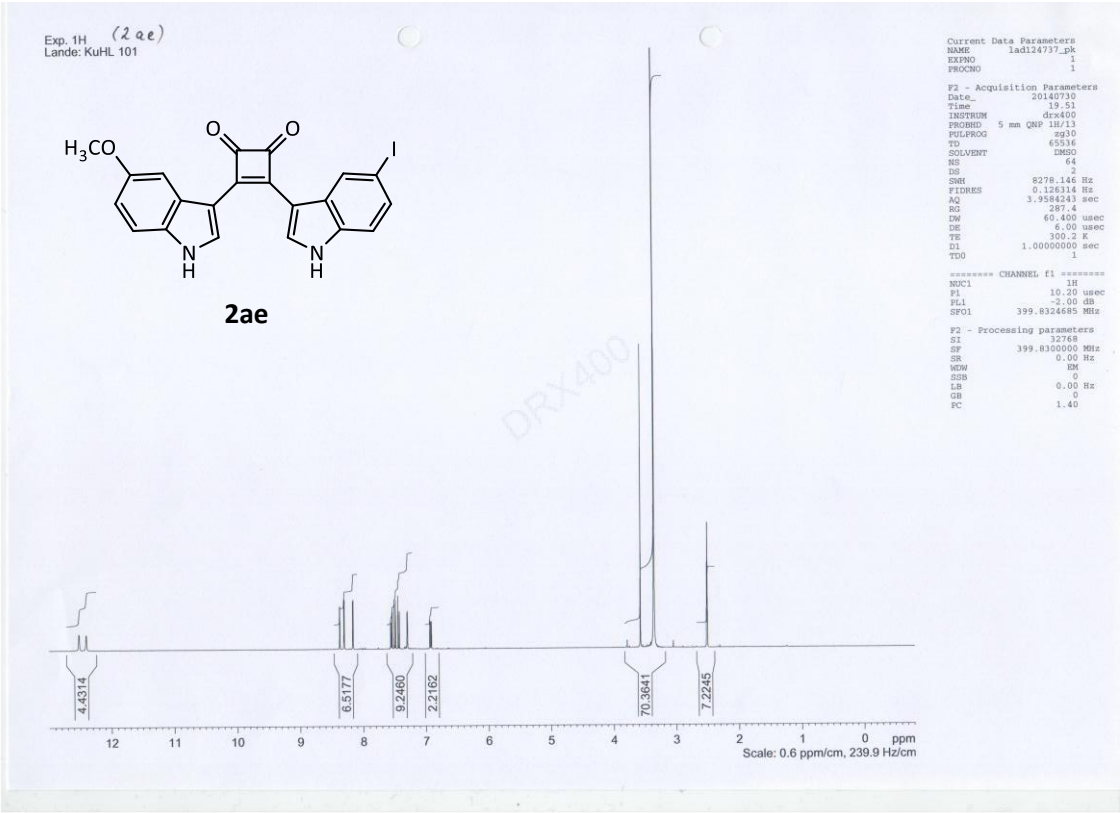

Exp. 1H
Lande: KuHL032 (2q)
protonepp.ibk DMSO {D:\u} nmr 2
2q
AVIII400
3.2683
35.2964
48.0533
10.8153
2.5667
ppm
Scale: 0.6435 ppm/cm, 257.6 Hz/cm

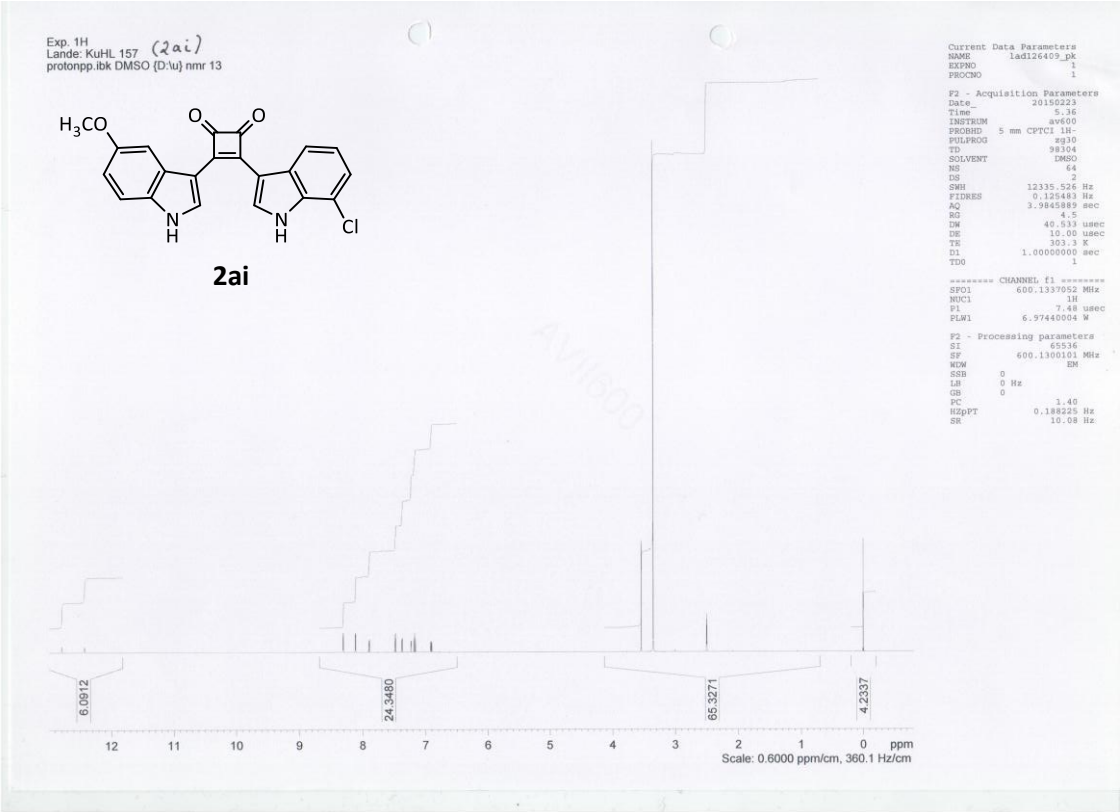

Exp. 1H
Lande: KUHL 117 (2r)
protonpp.ibk DMSO {D:\u} nmr 2
2r
9.7550
19.4963
24.3871
42.1777
4.1839
Scale: 0.6000 ppm/cm, 360.1 Hz/cm

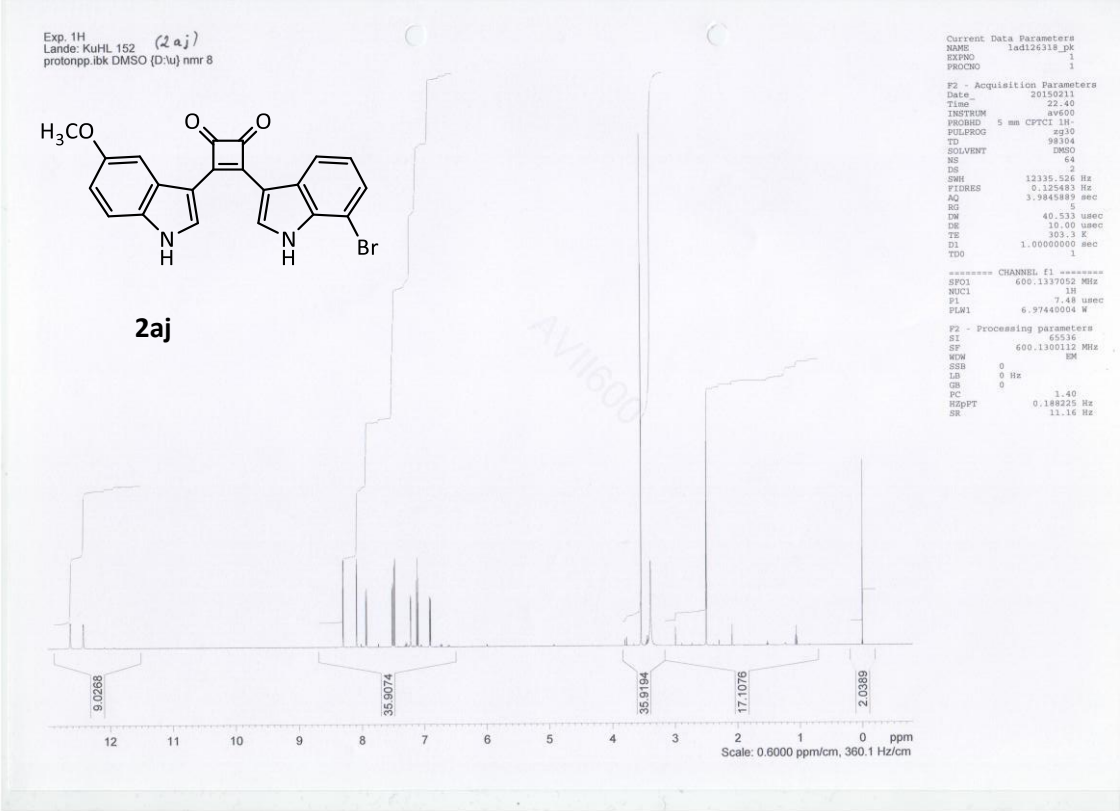

Exp. 1H
Lande: KuHL072 (72) (2u)
protonepp.ibk DMSO {D:\u} nmr 10
2u
3.2303
44.4145
52.3552
Scale: 0.6 ppm/cm, 360.1 Hz/cm

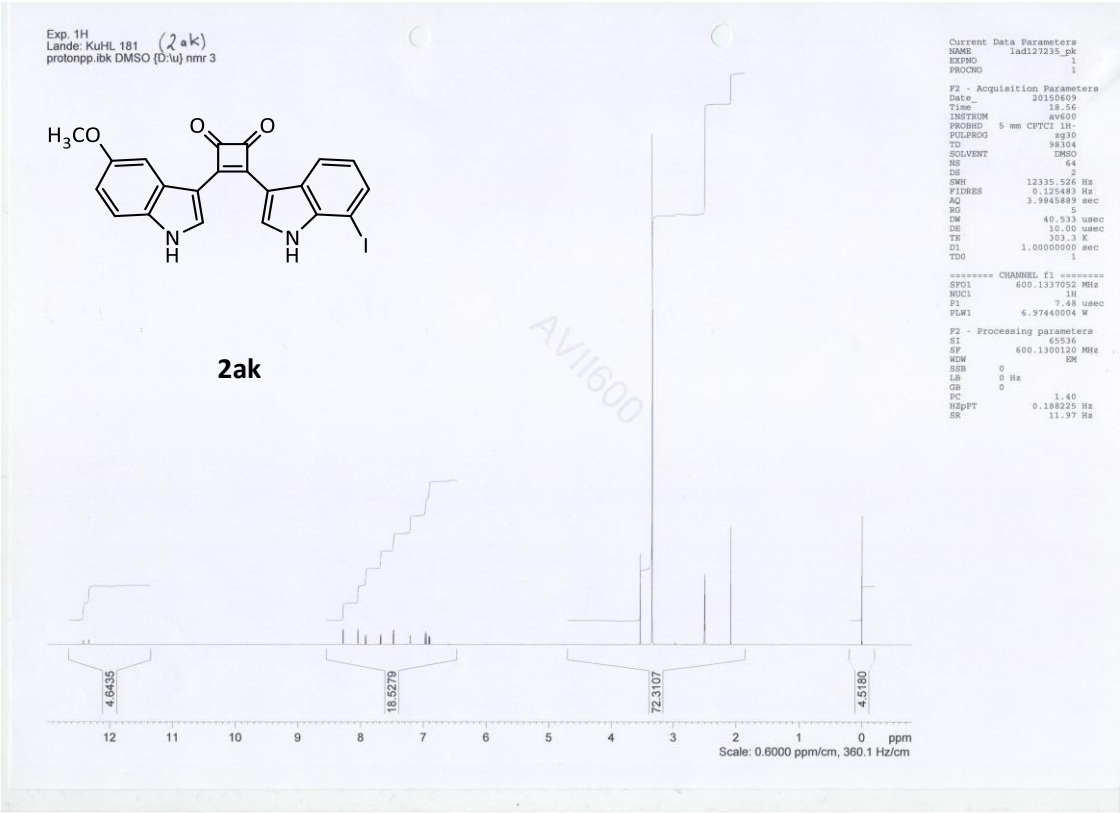

Exp. 1H
Lande: KuHL050 (2y)
protonepp.ibk DMSO {D:\u} nmr 16
2y
2.3054
9.4305
12.3635
48.8999
22.3670
4.6337
ppm
Scale: 0.6435 ppm/cm, 386.2 Hz/cm

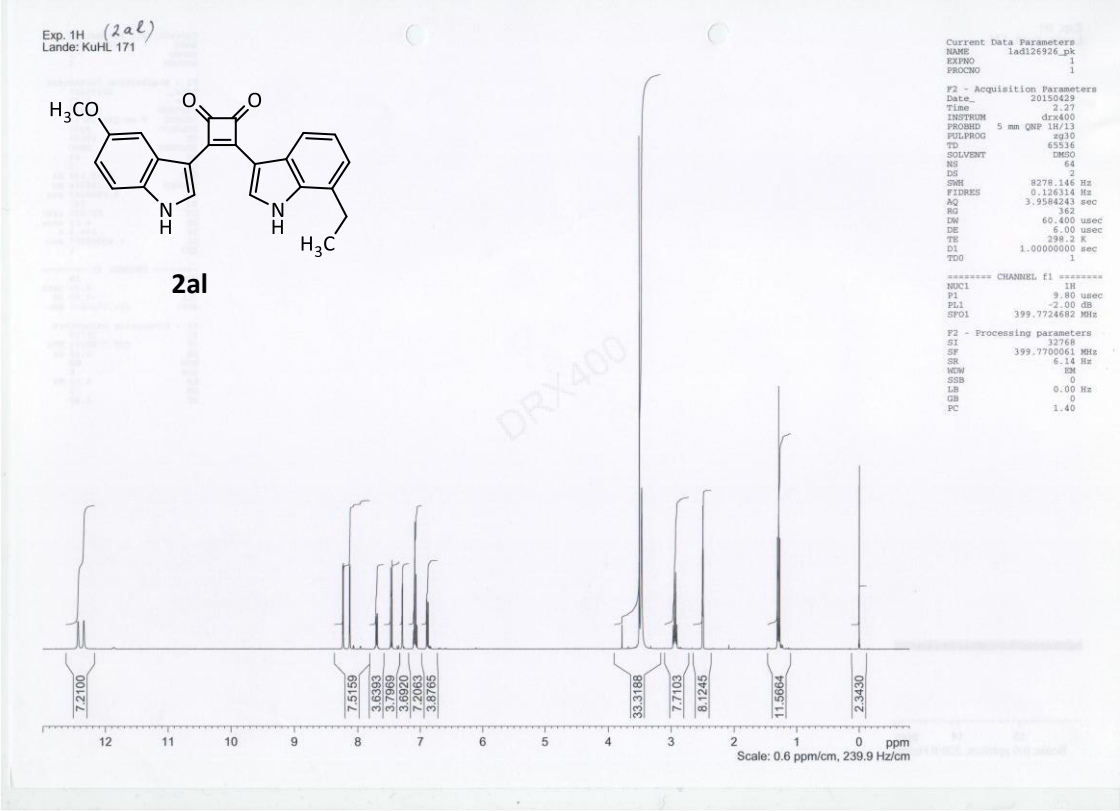

Exp. 1H
Lande: KuHL047 (2ad)
protonepp.ibk DMSO {D:\u} nmr 5
2ad
5.7249
23.7662
60.3148
10.1941
ppm
Scale: 0.6435 ppm/cm, 386.2 Hz/cm

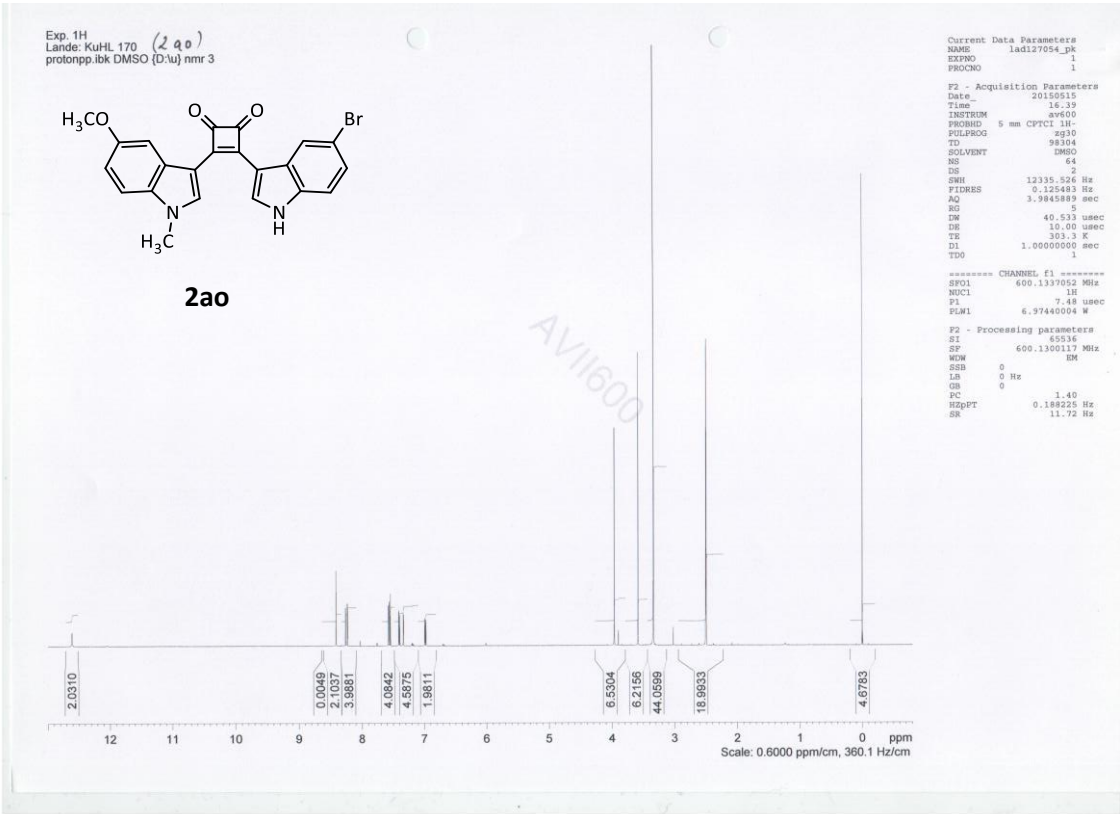

Exp. 1H (2ae)
Lande: KuHL 101
H3CO
O
O
I
N
H
N
H
2ae
4.4314
6.5177
9.2460
2.2162
70.3641
7.2245
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6 ppm/cm, 239.9 Hz/cm
Current Data Parameters
NAME lad124737_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140730
Time 19.51
INSTRUM drx400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 287.4
DW 60.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
PL1 -2.00 dB
SFO1 399.8324685 MHz
F2 - Processing parameters
SI 32768
SF 399.8300000 MHz
SR 0.00 Hz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
RC 1.40
DRX400


Exp. 1H
Lande: KuHL 157 (2ai)
protonpp.ibk DMSO {D:\u} nmr 13
H3CO
O
O
N
H
N
H
Cl
2ai
6.0912
24.3480
65.3271
4.2337
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6000 ppm/cm, 360.1 Hz/cm
Current Data Parameters
NAME lad126409_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150223
Time 5.36
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 98304
SOLVENT DMSO
NS 64
DS 2
SWH 12335.526 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 4.5
DW 40.533 usec
DE 10.00 usec
TE 303.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1337052 MHz
NUC1 1H
P1 7.48 usec
PLW1 6.97440004 W
F2 - Processing parameters
SI 65536
SF 600.1300101 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.40
HZpPT 0.188225 Hz
SR 10.08 Hz
AVIII600


Exp. 1H
Lande: KuHL 152 (2aj)
protonpp.ibk DMSO {D:\u} nmr 8
H3CO
O
O
N
H
N
H
Br
2aj
9.0268
35.9074
35.9194
17.1076
2.0389
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6000 ppm/cm, 360.1 Hz/cm
Current Data Parameters
NAME lad126318_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150211
Time 22.40
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 98304
SOLVENT DMSO
NS 64
DS 2
SWH 12335.526 Hz
FIDRES 0.125493 Hz
AQ 3.9845889 sec
RG 5
DW 40.533 usec
DE 10.00 usec
TE 303.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1337052 MHz
NUC1 1H
P1 7.48 usec
PLW1 6.97440004 W
F2 - Processing parameters
SI 65536
SF 600.1300112 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.40
HZPPT 0.188225 Hz
SR 11.16 Hz


Exp. 1H
Lande: KuHL 181 (2ak)
protonpp.ibk DMSO {D:\u} nmr 3
H3CO
O
O
N
H
N
H
I
2ak
4.6435
18.5279
72.3107
4.5180
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6000 ppm/cm, 360.1 Hz/cm
Current Data Parameters
NAME lad127235_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150609
Time 18.56
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 98304
SOLVENT DMSO
NS 64
DS 2
SWH 12335.526 Hz
FIDRES 0.125493 Hz
AQ 3.9845889 sec
RG 5
DW 40.533 usec
DE 10.00 usec
TE 303.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1337052 MHz
NUC1 1H
P1 7.48 usec
PLW1 6.97440004 W
F2 - Processing parameters
SI 65536
SF 600.1300120 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.40
HZPPT 0.188225 Hz
SR 11.97 Hz


Exp. 1H (2al)
Lande: KuHL 171
H3CO
O
O
N
H
N
H
H3C
2al
7.2100
7.5159
3.6393
3.7969
3.6920
7.2063
3.8765
33.3188
7.7103
8.1245
11.5664
2.3430
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6 ppm/cm, 239.9 Hz/cm
Current Data Parameters
NAME lad126926_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150429
Time 2.27
INSTRUM drx400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
PL1 -2.00 dB
SFO1 399.7724682 MHz
F2 - Processing parameters
SI 32768
SF 399.7700061 MHz
SR 6.14 Hz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
DRX400


Exp. 1H
Lande: KuHL 170 (2ao)
protonpp.ibk DMSO {D:\u} nmr 3
H3CO
O
O
Br
N
H3C
N
H
2ao
2.0310
0.0049
2.1037
3.9881
4.0842
4.5875
1.9811
6.5304
6.2156
44.0599
18.9933
4.6783
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
Scale: 0.6000 ppm/cm, 360.1 Hz/cm
Current Data Parameters
NAME lad127054_pk
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150515
Time 16.39
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 98304
SOLVENT DMSO
NS 64
DS 2
SWH 12335.526 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 5
DW 40.533 usec
DE 10.00 usec
TE 303.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1337052 MHz
NUC1 1H
P1 7.48 usec
PLW1 6.97440004 W
F2 - Processing parameters
SI 65536
SF 600.1300117 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.40
HZpPT 0.188225 Hz
SR 11.72 Hz
AVII600

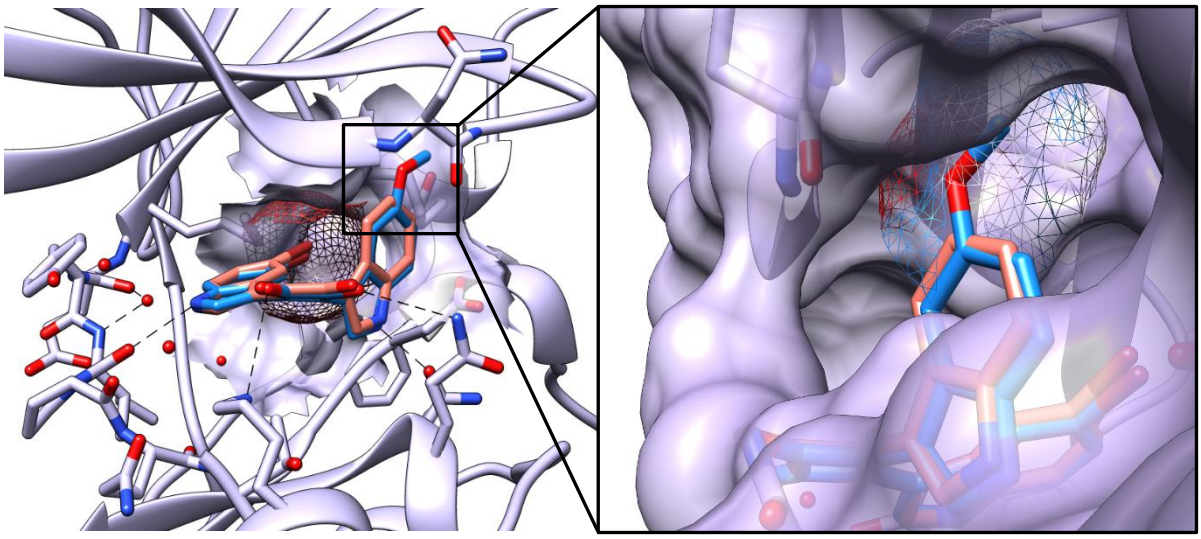


Figure S1: Suggested orientation generated by docking of **2b** (orange) and of **2ad** (blue) in the ATP binding pocket of a *Pf*GSK-3 homology model (light purple). While the nitrogen of the bromo-substituted indole ring acts as hydrogen bond donor to the hinge area, the bromo substituent occupies a hydrophobic back pocket. The second indole ring is orientated perpendicular. Detail shown on the right: The methoxy group of **2ad** fills a pocket at the roof of the ATP binding site. Although the results of these docking experiments could very well explain the antiplasmodial effect of the binsindoloylcyclobutenediones reported here, the enzymatic assays later showed that *Pf*GSK-3 is not the relevant biological target of this class of compounds.