Synthesis of new pyridazino[4,5-b]indol-4-ones and pyridazin-3(2H)-one analogs as DYRK1A inhibitors

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Amélie Bruel[a], Romain Bénéteau[a], Mylène Chabanne[a], Olivier Lozach[b], Rémy Le Guevel[c], Myriam Ravache[c], Hélène Bénédetti[d], Laurent Meijer[b,e], Cédric Logé[a,*], Jean-Michel Robert[a]

[a] *Université de Nantes, Nantes Atlantique Universités, Laboratoire de Chimie Thérapeutique, Cibles et Médicaments des Infections et du Cancer, IICIMED-EA 1155, UFR Sciences Pharmaceutiques, 1 rue Gaston Veil, Nantes F-44035 Cedex 1, France*
[b] *Protein Phosphorylation & Human Disease group, CNRS, USR 3151, Station Biologique, B.P. 74, 29682 Roscoff Cedex, France*
[c] *Plate-forme ImPACcell, UMS-3480, Université de Rennes 1, Campus de Villejean, 2 avenue du Professeur Léon Bernard, 35043 Rennes Cedex, France*
[d] *Centre de Biophysique Moléculaire, CNRS, UPR 4301, Université d'Orléans et INSERM, rue Charles Sadron, 45071 Orléans Cedex 2, France*
[e] *ManRos Therapeutics, Centre de Perharidy, 29680 Roscoff, France*

Abstract : New pyridazino[4,5-*b*]indol-4-ones and pyridazin-3(2*H*)-one analogs were synthesized and their inhibitory activities against DYRK1A, CDK5/p25, GSK3α/β and p110-α isoform of PI3K evaluated using harmine as reference. Both furan-2-yl **10** and pyridin-4-yl **19** from the two different series, exhibited submicromolar IC_{50} against DYRK1A with no activities against the three other kinases. In addition, compound **10** exhibited antiproliferative activities in the Huh-7, Caco2 and MDA-MB-231 cell lines.

Harmine and other members of the family of β-carboline alkaloids have been shown to inhibit the dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), a serine/threonine kinase implicated in Down syndrome, and to reduce the levels of multiple phosphorylated forms of tau protein that are important in the pathological progression of Alzheimer's disease (AD).[1-3] DYRK1A belongs to the DYRK family within the CMGC group (cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAP kinases), glycogen synthase kinases (GSK) and CDK-like kinases (CLKs)) of the eukaryote kinome. Although harmine represents a standard in terms of activity and selectivity, the numerous side effects have led to the development and study of various natural and synthetic compounds, a number of them incorporating indolic or aza-indolic scaffolds (see meridianin, meriolin and lamellarin derivatives).[4] In particularly, harmine and derivatives exhibited cytotoxic activities against human cancer cell lines that could be (partly) attributed to its planar tricyclic system able to intercalate DNA.[5,6]

Previously, as an initial attempt to design new kinase inhibitors focused on a pyridazino[4,5-*b*]indol-4-one scaffold, we already prepared compound **1** showing micromolar IC_{50} value against DYRK1A (Fig. 1).[7] Due to its structural analogy with harmine, we thought that this molecule could be a good starting template for further optimization. Thus, we focused our efforts on the introduction of various (het)aryl substituents at position 1 of this privileged structure and compared the biological results with some of their non-planar analogs derived from a pyridazin-3(2*H*)-one scaffold (Fig. 1).

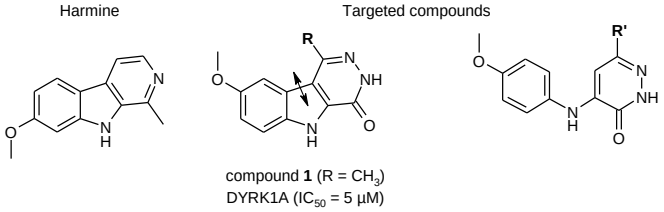
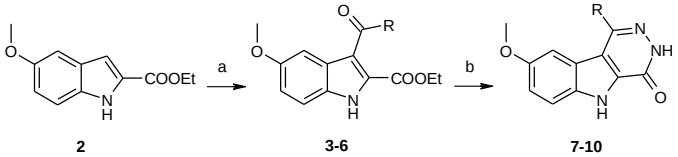


Figure 1. General structures of synthesized compounds.

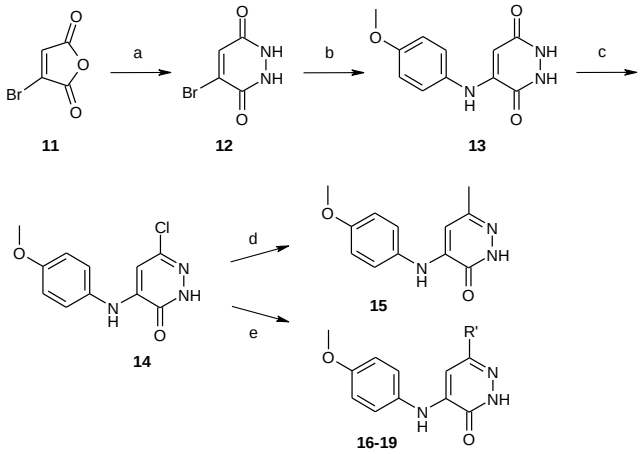
Pyridazino[4,5-b]indol-4-ones **7-10** were classically prepared starting from ethyl 5-methoxy-1*H*-indole-2-carboxylate. Friedel-Crafts acylation using a wide variety of acid chlorides in the presence of Tin(IV) chloride in methylene chloride-nitromethane gave indoles **3-6** which were cyclized with hydrazine hydrate in ethanolic solution to afford the expected tricyclic compounds (Scheme 1).[8,9]



Scheme 1. *Reagents and conditions*: (a) $SnCl_4$, RCOCl, CH_2Cl_2, CH_3NO_2, rt or reflux, 5-20 h, 28-48%; (b) Hydrazine hydrate, EtOH, rt or reflux, 10-72 h, 38-49%.

* Corresponding author. Tel.: +33 (0)240411108; fax: +33 (0)240412876; e-mail: cedric.loge@univ-nantes.fr (C. Logé)

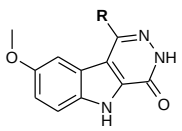
Pyridazin-3(2*H*)-ones **15**-**19** can be prepared from bromomaleic anhydride, which reacted with hydrazine sulfate in water under refluxing conditions, to give 4-bromo-1,2-dihydropyridazine-3,6-dione (**12**) in 89% yield.[10] Condensation of *p*-anisidine with compound **12**, in the presence of copper powder, in *N*-methyl-2-pyrrolidone (NMP) at 160°C led to compound **13** which can be monochlorinated at the C-6 position with excess phosphorus oxychloride ($POCl_3$) at 100°C during one hour to give intermediate **14**.[11,12] Introduction of a methyl substituent (**15**) was successful with trimethylaluminium under $Pd(PPh_3)_4$ catalyzed conditions in refluxing dioxane[13] whereas Suzuki cross-coupling with various boronic acids or pyridine-4-boronic acid pinacol ester, under microwave irradiation, afforded molecules **16**-**19** (Scheme 2).[14]



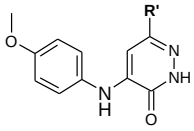
Scheme 2. *Reagents and conditions*: (a) Hydrazine sulfate, H_2O, reflux, 10 h, 89%; (b) *p*-anisidine, Cu_{cat}, NMP, 160°C, 4 h, 87%; (c) $POCl_3$ (6éq), 100°C, 1 h, 81%; (d) $AlMe_3$, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 24 h, 20%; (e) Boronic acids or pyridine-4-boronic acid pinacol ester, Na_2CO_3 (2M), $Pd(PPh_3)_4$, toluene or DMF, 110°C (mW), 15-35 min, 20-82%.

The final products were tested against four representative kinases DYRK1A, CDK5/p25, GSK3α/β and p110-α isoform of PI3K chosen for their involvement in regulation processes including neurodegenerative diseases or cancer (Table 1).[7,15] The biological results are very heterogeneous, except on CDK5/p25 where all the compounds displayed IC_{50} values above 10 µM. In the pyridazino[4,5-*b*]indol-4-one series (**7**-**10**), compound **10** bearing a furan-2-yl substituent showed a significant submicromolar IC_{50} value of 0.22 µM against DYRK1A, only 4-fold less active than harmine, with no activity towards the other kinases. From this data alone, it appears that particular variations at position 1 of the pyridazino[4,5-b]indol-4-one scaffold seem to be allowed for a good inhibitory activity against this enzyme, although the results observed for compounds **7**-**9** are contradictory. Also, when we compared compounds **1** and **10** with their ring-opened analogs **15** and **18** from the pyridazin-3(2*H*)-one series, a loss of activity was observed while the unique compound **19** containing a pyridine moiety at position 6 of the pyridazin-3(2*H*)-one series displayed a pronounced inhibitory activity against DYRK1A (IC_{50} = 0.61 µM). Such structure-activity relationships are difficult to interpret and it is plausible that different binding modes in the ATP binding site are involved depending upon the substituent and the capacity of these compounds to form multiple hydrogen bonds with the hinge region.

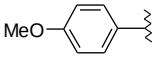
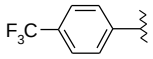
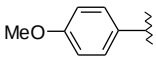
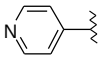
Table 1. Kinase inhibition (IC_{50} values in µM; NT = not tested; values lower than 10 µM are highlighted in bold).



1, 7-10



15-19

Compounds	R	R'	DYRK1A	CDK5/p25	GSK3α/β	PI3Kα
1	CH_3		**5**	>10	>10	NT
7			>10	NT	**1.3**	>10
8			**1.5**	>10	**1.4**	>10
9			>10	>10	>10	**6.9**
10			**0.22**	>10	>10	>10
15		CH_3	>10	>10	>10	NT
16			>10	>10	>10	>10
17			**5.1**	>10	**2.5**	NT
18			>10	>10	>10	>10
19			**0.61**	>10	**9.6**	>10
Harmine			**0.06**	**8**	>10	NT

A purely hypothetical binding mode for the most efficient compound **10** inside the ATP-binding site of DYRK1A (pdb code: 2WO6) is shown in Figure 2.[16,17] In contrast to harmine which interacts with residue Leu241 (hinge region) *via* a key hydrogen bond to its methoxy group,[18] compound **10** appears to involve its pyridazinone ring through hydrogen bonds with the hinge region (backbone atoms of Glu239 and Leu241), thereby positioning the five-membered aromatic furan ring in a π-π stacking interaction with the gatekeeper residue (Phe238). Selectivity over CDK5 and GSK3 could be attributed to an additional direct or water-mediated hydrogen bond interaction between the methoxy group and the asparagine residue (Asn244) located in the pocket of the kinase (Asp86 in CDK5; Thr138 in GSK3).

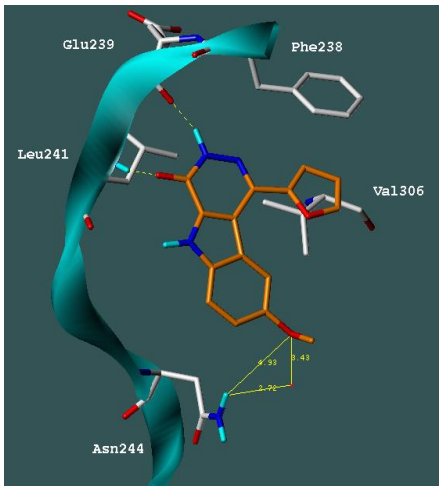


Figure 2. Docking model of compound **10** into the ATP site of DYRK1A.

The cytotoxic effects of these compounds were then determined against six human cancer cell lines (hepatocellular carcinoma Huh-7, colorectal adenocarcinoma Caco2, colorectal carcinoma HCT-116, breast carcinoma MDA-MB-231, prostate carcinoma PC3 and lung carcinoid NCI-H727) and one normal cell line (fibroblasts) (Table 2).[7] Only compound **10** exhibited anti-proliferative activities in the Huh-7, Caco2 and MDA-MB-231 cell lines with an IC_{50} value lower than 1 µM, probably by exerting a cytostatic effect, while other compounds had no effect on cell proliferation. However, these anti-proliferative effects may not be correlated with the compounds' ability to inhibit the DYRK1A protein kinase as compounds **8** or **19** were inactive on these cell lines.

Table 2. Anti-proliferative activity in various cell lines (IC_{50} values in µM; NT = not tested; values lower than 1 µM are highlighted in bold; the number in brackets indicate the percentage of cell growth decrease).[a]

Compounds	Huh-7	Caco2	HCT-116	MDA-MB-231	PC3	NCI-H727	Fibroblasts
1	3	8	15	5	7	5	20
7	NT	NT	NT	NT	NT	NT	NT
8	> 25	> 25	> 25	> 25	> 25	> 25	> 25
9	> 25	> 25	> 25	> 25	> 25	> 25	> 25
10	**0.25 (50%)**	**0.6**	3 (50%)	**0.3 (50%)**	> 25	> 25	> 25
15	NT	NT	NT	NT	NT	NT	NT
16	> 25	> 25	> 25	> 25	> 25	> 25	> 25
17	NT	NT	NT	NT	NT	NT	NT
18	> 25	> 25	> 25	> 25	> 25	> 25	> 25
19	> 25	> 25	> 25	> 25	> 25	> 25	> 25

[a] Assays were performed in triplicate. Reference compounds used (not shown) were DMSO, taxol and doxorubicin.

DYRK1A has been shown to be expressed ubiquitously, and its functional role in cancer is still largely obscure. Therefore, the attractive inhibitory profiles of both compounds **10** and **19** (from the two different series) against DYRK1A and selected cancer cell growth make them candidates for further evaluations (i.e. a screen against a wide variety of kinases to get an overall view of their selectivity), even if biological results for the pyridazino[4,5-*b*]indol-4-one scaffold (**10**) are probably due to combined interactions with several relevant targets that could imply undesirable side-effects.

Acknowledgments

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References and notes

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8. Synthesis of *Ethyl 3-(furan-2-ylcarbonyl)-5-methoxy-1H-indole-2-carboxylate* (**6**). To a cold solution of ethyl 5-methoxy-1*H*-indole-2-carboxylate (**2**) (500 mg, 2.28 mmol) in freshly distilled dichloromethane (10 mL)/nitromethane (4 mL) was added Tin(IV) chloride (2.7 mL, 2.74 mmol) and dropwise furan-2-carbonyl chloride (0.27 mL, 2.74 mmol). The mixture was boiled under argon for 18 h, then poured into ice-cold water and extracted with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product **6** (28% yield, off-white solid) which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 1.02 (t, 3H, ^3J = 7.1 Hz), 3.79 (s, 3H), 4.35 (q, 2H, ^3J = 7.1 Hz), 6.75 (dd, 1H, ^3J = 3.6 Hz, ^4J = 1.6 Hz), 7.04 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.4 Hz), 7.14 (d, 1H, ^3J = 2.4 Hz), 7.21 (dd, 1H, ^3J = 3.6 Hz, ^4J = 0.8 Hz), 7.48 (d, 1H, ^3J = 8.8 Hz), 8.00 (dd, 1H, ^3J = 3.6 Hz, ^4J = 0.8 Hz), 12.53 (s, 1H). IR (KBr cm^{-1}): 3448-3236 (υ NH), 1692 (υ C=O), 1639 (υ C=O).
9. Synthesis of *1-(furan-2-yl)-8-Methoxy-4-oxo-3,4-dihydro-5H-pyridazino[4,5-b]indole* (**10**). To a stirred solution of Ethyl 3-(furan-2-ylcarbonyl)-5-methoxy-1H-indole-2-carboxylate (**6**) (200 mg, 0.64 mmol) in EtOH (6 mL) was added dropwise hydrazine hydrate (0.062 mL, 1.28 mmol). After being stirred at room temperature for 10 h, the solution was concentrated under reduced pressure. The residue was washed with 1N HCl, filtered and purified on silica gel column chromatography (dichloromethane/methanol 10/1) to give compound **10** (38% yield, off-white solid). mp > 300°C; ^{1}H NMR (DMSO-d_6): δ 3.84 (s, 3H), 6.82 (m, 1H), 7.03 (d, 1H, ^3J = 3.2 Hz), 7.23 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.4 Hz), 7.58 (d, 1H, ^4J = 2.4 Hz), 7.60 (d, 1H, ^3J = 9.0 Hz), 8.13 (m, 1H), 12.86 (s, 1H), 13.00 (s, 1H). ^{13}C (100.6 MHz, DMSO-d_6) δ 155.15, 154.81, 150.23, 143.92, 135.40, 134.45, 132.55, 121.08, 117.59, 114.80, 114.09, 112.36, 109.86, 104.36, 55.41. IR (KBr cm^{-1}): 3455-3225 (υ NH), 1671 (υ C=O). MS (ESI) *m/z* (%): 282.1 $[M+H]^+$; UPLC purity 100%.
10. Synthesis of *4-bromo-1,2-dihydropyridazine-3,6-dione* (**12**). To a solution of hydrazine sulfate (6.5 g, 50 mmol) in water (70 mL) was added bromomaleic anhydride (**11**) (4.6 mL, 50 mmol). The mixture was heated under reflux for 10 h. After cooling, the crude product was filtered, washed with acetone and dried over reduced pressure to give compound **12** (89% yield, white solid). mp > 270°C; ^{1}H NMR (DMSO-d_6): δ 7.64 (s, 1H), 11.19 (s, 1H), 12.39 (s, 1H). IR (KBr cm^{-1}): 1638 (υ C=O).

11. Synthesis of *4-[(4-methoxyphenyl)amino]-1,2-dihydropyridazine-3,6-dione* (**13**). To a solution of 4-bromo-1,2-dihydropyridazine-3,6-dione (**12**) (3.0 g, 15.71 mmol) in *N*-methyl-2-pyrrolidone (8 mL) was added *p*-anisidine (3.87 g, 31.42 mmol) and copper powder (10 mg, 0.16 mmol). The resulting mixture was heated at 160°C for 4 h. After cooling, the mixture was basified with NaOH 1M, washed with ethyl acetate and then acidified by dropwise addition of concentrated HCl. The precipitate was filtered, triturated with ether and dried over reduced pressure to give compound **13** (87% yield, brown solid). mp = 256°C; ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H), 6.01 (s, 1H), 6.98 (d, 2H, ^{3}J = 9.0 Hz), 7.25 (d, 2H, ^{3}J = 9.0 Hz), 8.13 (s, 1H) and two NH are not visible. ^{13}C (100.6 MHz, DMSO-d_6) δ 156.28, 156.06 (2C), 142.77, 132.15, 124.03 (2C), 114.62 (2C), 92.30, 55.43. MS (ESI) *m/z* (%): 234.0 $[M+H]^+$; UPLC purity 95%.
12. Synthesis of *6-chloro-4-[(4-methoxyphenyl)amino]pyridazin-3(2H)-one* (**14**). A mixture of 4-[(4-methoxyphenyl)amino]-1,2-dihydropyridazine-3,6-dione (**13**) (3.0 g, 12.86 mmol) in $POCl_3$ (7.2 mL, 77.18 mmol) was heated at 100°C for 1 h. After cooling, the reaction mixture was poured into an ice-cold 1N NaOH solution and neutralized with concentrated HCl. The crude product was extracted with ethyl acetate. Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (dichloromethane/methanol 98/2) to give compound **14** (81% yield, off-white solid). ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H), 6.34 (s, 1H), 7.01 (d, 2H, ^{3}J = 8.8 Hz), 7.31 (d, 2H, ^{3}J = 8.8 Hz), 8.98 (s, 1H), 12.93 (s, 1H). ^{13}C (100.6 MHz, DMSO-d_6) δ 156.79, 156.07, 143.28, 139.92, 131.02, 124.82 (2C), 114.76 (2C), 98.88, 55.46. IR (KBr cm^{-1}): 3239 (υ NH), 1659 (υ C=O). MS (ESI) *m/z* (%): 252.0 $[M+H]^+$; 254.0 $[M+H+2]^+$ (Cl isotope); UPLC purity 97%.
13. Synthesis of *4-[(4-methoxyphenyl)amino]-6-methylpyridazin-3(2H)-one* (**15**). To a solution of 6-chloro-4-[(4-methoxyphenyl)amino]pyridazin-3(2H)-one (**14**) (100 mg, 0.4 mmol) in dry 1,4-dioxane (3 mL) under a nitrogen atmosphere were added tetrakis(triphenylphosphine)palladium (23 mg, 0.019 mmol) and trimethylaluminium (0.4 mL, 0.8 mmol). The resulting mixture was heated under reflux for 24 h. After cooling and adding water, the crude product was extracted with ethyl acetate. Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (petroleum ether/ethyl acetate 90/10) to give compound **15** (20% yield, off-white solid). ^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H), 3.79 (s, 3H), 6.42 (s, 1H), 6.98 (d, 2H, ^{3}J = 8.8 Hz), 7.29 (d, 2H, ^{3}J = 8.8 Hz), 8.41 (s, 1H), 12.53 (s, 1H). ^{13}C (100.6 MHz, DMSO-d_6) δ 156.73, 156.11, 146.15, 141.22, 132.18, 123.86 (2C), 114.72 (2C), 100.14, 55.56, 21.05. IR (KBr cm^{-1}): 3449 (υ NH), 1640 (υ C=O). MS (ESI) *m/z* (%): 232.1 $[M+H]^+$; UPLC purity 99%.
14. Synthesis of *4-[(4-methoxyphenyl)amino]-6-(pyridine-4-yl)pyridazin-3(2H)-one* (**19**). To a 10 mL vial under argon were added 6-chloro-4-[(4-methoxyphenyl)amino]pyridazin-3(2H)-one (**14**) (150 mg, 0.6 mmol), pyridine-4-boronic acid pinacol ester (183 mg, 0.89 mmol), tetrakis(triphenylphosphine)palladium (34 mg, 0.029 mmol), 2M Na_2CO_3 aqueous solution (0.6 mL) and dry DMF (3 mL). The resulting mixture was heated at 110 °C under microwave irradiation (100W) for 20 min. After cooling and adding water, the crude product was extracted with ethyl acetate. Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (dichloromethane) to give compound **19** (20% yield, off-white solid). ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H), 7.01 (s, 1H), 7.02 (d, 2H, ^{3}J = 8.8 Hz), 7.40 (d, 2H, ^{3}J = 8.8 Hz), 7.75 (d, 2H, ^{3}J = 5.8 Hz), 8.66 (d, 2H, ^{3}J = 5.8 Hz), 8.78 (s, 1H), 13.19 (s, 1H). ^{13}C (100.6 MHz, DMSO-d_6) δ 156.84, 156.31, 150.33 (2C), 143.74, 143.56, 141.96, 131.70, 124.25 (2C), 120.28 (2C), 114.73 (2C), 96.26, 55.43. IR (KBr cm^{-1}): 3200 (υ NH), 1647 (υ C=O). MS (ESI) *m/z* (%): 295.1 $[M+H]^+$; UPLC purity 94%.
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17. Molecular modeling studies were performed using Sybyl software version 8.0 running on a dell precision T3400 workstation. The structure of DYRK1A in complex with a consensus substrate (PDB code, 2WO6) was used as the template. Flexible docking of compound **10** into the ATP-binding site was performed using GOLD software. For each compound, the most stable docking model was selected according to the best scored conformation predicted by the GoldScore scoring function.
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Supplementary Material

^{1}H and ^{13}C NMR spectra for compounds **10** and **19** can be found in the online version.