Regioselective microwave synthesis and derivatization of 1,5-diaryl-3-amine-1,2,4-triazoles and a study of their cholinesterase inhibition properties.

Sabrina Neves Santos,\textsuperscript{a,b} Gabriela Alves de Souza,\textsuperscript{a,b} Thiago Moreira Pereira,\textsuperscript{a,b} Daiana Portella Franco,\textsuperscript{a,b} Catarina de Nigris Del Cistia,\textsuperscript{b} Carlos Mauricio R. Sant'Anna,\textsuperscript{b} Renata Barbosa Lacerda,\textsuperscript{a,b} and Arthur Eugen Kümmerle\textsuperscript{a,b}* 

\textsuperscript{a} Laboratório de Diversidade Molecular e Química Medicinal (LaDMol-QM, Molecular Diversity and Medicinal Chemistry Laboratory), Departament of Chemistry, Universidade Federal Rural do Rio de Janeiro, Seropédica, Rio de Janeiro, 239897-000, Brazil.

\textsuperscript{b} Programa de Pós-Graduação em Química (PPGQ), Universidade Federal Rural do Rio de Janeiro, Seropédica, Rio de Janeiro, 239897-000, Brazil.

* akummerle@hotmail.com

Supporting Information

Contents

Copies of $^1$H and $^{13}$C NMR ..........................................................2-37
Biological Evaluations .................................................................42-43
ADMET previsions .................................................................44-47
Fig. S1. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 1 in DMSO-d6.
Fig. S2. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 3 in CDCl$_3$. 
Fig. S3. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 5 in CDCl$_3$.

Original literature: Org. Lett. (2009) 11, 5482-5485.

ours: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08-8.06(d, 2H), 7.64-7.62(d, 2H), 7.56-7.52(t, 2H), 7.44-7.40(m, 4H), 4.80(br, 2H)
ours: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.47 (d, 2H), 7.39 – 7.28 (m, 10H), 4.27 (br s, 2H);

Fig. S4. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 6a in CDCl$_3$. 

Original literature: Org. Lett. (2015) 17, 4678-4681.
Fig. S5. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 6b in CDCl$_3$. 
Fig. S6. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 6c in CDCl$_3$. 
Fig. S7. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 6d in CDCl$_3$. 
Fig. S8. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 6e in CDCl$_3$
Fig. S9. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 6f in CDCl$_3$
Fig. S10. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 7a in CDCl$_3$
Fig. S11. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 7b in CDCl$_3$
Fig. S12. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 7c in CDCl$_3$
Fig. S13. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 7d in CDCl$_3$
Fig. S14. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 7e in CDCl$_3$
Fig. S15. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 7f in CDCl$_3$
Fig. S16. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 8 in DMSO-$d_6$. 

H$_2$N \[ \begin{array}{c} \text{S} \\ \text{N} \\ \text{O} \end{array} \]
Fig. S17. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9a in CDCl$_3$. 
Fig. S18. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9b in CDCl$_3$. 

Fig. S19. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9c in CDCl$_3$
Fig. S20. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9d in CDCl$_3$
Fig. S21. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9e in DMSO-$d_6$. 
Fig. S22. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 9f in CDCl$_3$. 
Fig. S23. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 9g in CDCl$_3$. 
Fig. S24. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 9h in CDCl$_3$. 
Fig. S25. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 10a in CDCl$_3$. 

$^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 10a in CDCl$_3$. 

Chemical Shift (ppm)

Normalized Intensity

CHLOROFORM-d

28.26
35.54
81.29
125.46
127.64
128.47
128.91
129.28
130.01
137.97
153.11
153.56
160.11
Fig. S26: $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10b in CDCl$_3$. 

Chemical Shift (ppm) and normalized intensity are shown in the graph.

Normalized Intensity

NMR spectrum of 10b in CDCl$_3$.
Fig. S27. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10c in CDCl$_3$. 

Normalized Intensity

Chemical Shift (ppm)

Normalized Intensity

Chemical Shift (ppm)
Fig. S2. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10d in CDCl$_3$. 

Fig. S28. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10d in CDCl$_3$. 
Fig. S29. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10e in CDCl$_3$
Fig. S30. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 10f in CDCl$_3$
Fig. S31. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 10g in CDCl$_3$
Fig. S32. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 10h in CDCl$_3$
Fig. S33. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 15a in CDCl$_3$
Fig. S34. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 15b in CDCl$_3$
Fig. S35. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 15c in CDCl$_3$
Fig. S36. $^1$H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 15d in CDCl$_3$. 

**Chemical Shift (ppm)**

**Normalized Intensity**

**Normalized Intensity**

**Chemical Shift (ppm)**
Fig. S37. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13a in CDCl$_3$
Fig. S38. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13b in CDCl$_3$
Fig. S39. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13c in CDCl$_3$
Fig. S40. $^1$H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13d in CDCl$_3$
Biological Results

Fig S41. Graphs of AChE inhibition percentage vs. inhibitor concentration

Fig S42. Graphs of BuChE inhibition percentage vs. inhibitor concentration
Table 1. Kinetic evaluations data for compound 13a

| Concentração (μM) | $V_{\text{máx}} \pm \text{DP}$ (μM/min) | $K_m \pm \text{DP}$ (μM) | $K_i$ (μM) ± DP$^a$ | $K_r$ (μM) ± DP$^b$ |
|-------------------|------------------------------------------|--------------------------|----------------------|---------------------|
| 13a (AChE)        |                                          |                          |                      |                     |
| 0                 | 13,24 ± 0,628                            | 51,60 ± 2,843            |                      |                     |
| 3                 | 5,12 ± 0,234                             | 106,17 ± 3,828           | 0,36 ± 0,008         | 1,29 ± 0,031        |
| 6                 | 3,20 ± 0,273                             | 121,05 ± 4,313           |                      |                     |
| 13a (BuChE)       |                                          |                          |                      |                     |
| 0                 | 11,51 ± 0,169                            | 70,12 ± 0,042            |                      |                     |
| 1                 | 9,92 ± 0,411                             | 116,25 ± 3,606           | 0,62 ± 0,013         | 2,00 ± 0,033        |
| 3                 | 6,27 ± 0,438                             | 180,60 ± 2,404           |                      |                     |

$^a$ inhibitory constant for competitive inhibition; $^b$ inhibitory constant for non-competitive inhibition; Data obtained ± standard deviation (SD) of triplicates from independent assays.
**ADMET previsions**

**Molecule 13a**

### Physicochemical Properties

| Property                  | Value                   |
|---------------------------|-------------------------|
| Molecular weight          | 452.59 g/mol            |
| Fraction Csp3             | 0.29                    |
| Num. rotatable bonds      | 9                       |
| Num. H-bond acceptors     | 4                       |
| Num. H-bond donors        | 1                       |
| Molar Refractivity        | 145.74                  |
| TPSA                      | 49.22 Å²                |

#### Lipophilicity

| Property                  | Value                   |
|---------------------------|-------------------------|
| Log $P_{ow}$ (iLOGP)      | 4.65                    |
| Log $P_{ow}$ (XLOGP3)     | 5.34                    |
| Log $P_{ow}$ (WLOGP)      | 3.45                    |
| Log $P_{ow}$ (MLOGP)      | 4.19                    |
| Log $P_{ow}$ (SILICOS-IT) | 3.71                    |
| Consensus Log $P_{ow}$    | 4.27                    |

#### Water Solubility

| Property                  | Value                   |
|---------------------------|-------------------------|
| Log $S$ (ESOL)            | -5.92                   |
| Solubility                | 5.48e-04 mg/ml ; 1.21e-06 mol/l |
| Class                     | Moderately soluble      |

#### Pharmacokinetics

| Property                  | Value                   |
|---------------------------|-------------------------|
| GI absorption             | High                    |
| BBB permeant              | Yes                     |
| CYP1A2 inhibitor          | No                      |
| CYP2C19 inhibitor         | Yes                     |
| CYP2C9 inhibitor          | Yes                     |
| CYP2D6 inhibitor          | Yes                     |
| CYP3A4 inhibitor          | Yes                     |

#### Druglikeness

| Property                  | Value                   |
|---------------------------|-------------------------|
| Lipinski                  | Yes; 1 violation: MLOGP>4.15 |
| Veber                     | Yes                     |
| Egan                      | Yes                     |
| Bioavailability Score     | 0.55                    |

#### Medicinal Chemistry

| Property                  | Value                   |
|---------------------------|-------------------------|
| PAINS                     | 0 alert                 |
| Brek                      | 0 alert                 |
| Leadlikeness              | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 |
| Synthetic accessibility   | 3.72                    |
### Molecule 13b

![Molecule 13b](image)

#### Physicochemical Properties

| Property                        | Value               |
|---------------------------------|---------------------|
| Molecular weight                | 466.62 g/mol        |
| Fraction Csp3                   | 0.31                |
| Num. rotatable bonds            | 10                  |
| Num. H-bond acceptors           | 4                   |
| Num. H-bond donors              | 1                   |
| Molar Refractivity              | 150.55              |
| TPSA                            | 49.22 Å²            |

#### Lipophilicity

| Property                        | Value               |
|---------------------------------|---------------------|
| $\log P_{ow}$ (iLOGP)           | 4.93                |
| $\log P_{ow}$ (XLOGP3)          | 5.70                |
| $\log P_{ow}$ (WLOGP)           | 3.84                |
| $\log P_{ow}$ (MLOGP)           | 4.39                |
| $\log P_{ow}$ (SILICOS-IT)      | 4.10                |
| Consensus $\log P_{ow}$         | 4.59                |

#### Water Solubility

| Property                        | Value               |
|---------------------------------|---------------------|
| $\log S$ (ESOL)                 | -6.15               |
| Solubility                      | 3.30e-04 mg/ml ; 7.07e-07 mol/l |
| Class                           | Poorly soluble      |

#### Pharmacokinetics

| Property                        | Value               |
|---------------------------------|---------------------|
| GI absorption                   | High                |
| BBB permeant                    | Yes                 |
| CYP1A2 inhibitor                | No                  |
| CYP2C19 inhibitor               | Yes                 |
| CYP2C9 inhibitor                | Yes                 |
| CYP2D6 inhibitor                | Yes                 |
| CYP3A4 inhibitor                | Yes                 |

#### Druglikeness

| Property                        | Value               |
|---------------------------------|---------------------|
| Lipinski                        | Yes; 1 violation: MLOGP>4.15 |
| Veber                           | Yes                 |
| Egan                            | Yes                 |
| Bioavailability Score           | 0.55                |

#### Medicinal Chemistry

| Property                        | Value               |
|---------------------------------|---------------------|
| PAINS                           | 0 alert             |
| Brenk                           | 0 alert             |
| Leadlikeness                    | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 |
| Synthetic accessibility         | 3.79                |
**Molecule 13c**

![Molecule Image](image)

| Physicochemical Properties | Value |
|----------------------------|-------|
| Molecular weight          | 480.65 g/mol |
| Fraction Csp3             | 0.33   |
| Num. rotatable bonds      | 11     |
| Num. H-bond acceptors     | 4      |
| Num. H-bond donors        | 1      |
| Molar Refractivity        | 155.36 |
| TPSA                      | 49.22 Å² |

| Lipophilicity             | Value |
|----------------------------|-------|
| Log $P_{ow}$ (iLOGP)      | 5.13  |
| Log $P_{ow}$ (XLOGP3)     | 6.06  |
| Log $P_{ow}$ (WLOGP)      | 4.23  |
| Log $P_{ow}$ (MLOGP)      | 4.58  |
| Log $P_{ow}$ (SILICOS-IT) | 4.50  |
| Consensus Log $P_{ow}$    | 4.90  |

| Water Solubility          | Value          |
|----------------------------|----------------|
| Log $S$ (ESOL)            | -6.38          |
| Solubility                | 1.98e-04 mg/ml ; 4.12e-07 mol/l |
| Class                     | Poorly soluble |

| Pharmacokinetics          | Value          |
|----------------------------|----------------|
| GI absorption             | High           |
| BBB permeant              | Yes            |
| CYP1A2 inhibitor          | Yes            |
| CYP2C19 inhibitor         | Yes            |
| CYP2C9 inhibitor          | No             |
| CYP2D6 inhibitor          | Yes            |
| CYP3A4 inhibitor          | Yes            |

| Druglikeness               | Value          |
|----------------------------|----------------|
| Lipinski                   | Yes; 1 violation: MLOGP>4.15 |
| Veber                      | No; 1 violation: Rotors>10 |
| Egan                       | Yes            |
| Bioavailability Score      | 0.55           |

| Medicinal Chemistry        | Value          |
|----------------------------|----------------|
| PAINS                      | 0 alert        |
| Brenk                      | 0 alert        |
| Leadlikeness               | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 |
| Synthetic accessibility    | 3.88           |
### Molecule 13d

![Molecule 13d](image)

#### Physicochemical Properties

| Property                        | Value                        |
|--------------------------------|------------------------------|
| Molecular weight               | 494.67 g/mol                 |
| Fraction Csp3                  | 0.35                         |
| Num. rotatable bonds           | 12                           |
| Num. H-bond acceptors          | 4                            |
| Num. H-bond donors             | 1                            |
| Molar Refractivity             | 160.17                       |
| TPSA                           | 49.22 Å²                     |

#### Lipophilicity

| Property                        | Value          |
|--------------------------------|----------------|
| Log $P_{ow}$ (iLOGP)            | 5.21           |
| Log $P_{ow}$ (XLOGP3)           | 6.41           |
| Log $P_{ow}$ (WLOGP)            | 4.62           |
| Log $P_{ow}$ (MLOGP)            | 4.77           |
| Log $P_{ow}$ (SILICOS-IT)       | 4.90           |
| Consensus Log $P_{ow}$          | 5.18           |

#### Water Solubility

| Property                        | Value                        |
|--------------------------------|------------------------------|
| Log $S$ (ESOL)                  | -6.61                        |
| Solubility                      | 1.21e-04 mg/ml ; 2.44e-07 mol/l |
| Class                           | Poorly soluble               |

#### Pharmacokinetics

| Property                        | Value |
|--------------------------------|-------|
| GI absorption                  | High  |
| BBB permeant                   | Yes   |
| CYP1A2 inhibitor               | Yes   |
| CYP2C19 inhibitor              | Yes   |
| CYP2C9 inhibitor               | No    |
| CYP2D6 inhibitor               | Yes   |
| CYP3A4 inhibitor               | Yes   |

#### Druglikeness

| Property                        | Value                                      |
|--------------------------------|--------------------------------------------|
| Lipinski                       | Yes; 1 violation: MLOGP>4.15               |
| Veber                          | No; 1 violation: Rotors>10                 |
| Egan                           | Yes                                        |
| Bioavailability Score          | 0.55                                       |

#### Medicinal Chemistry

| Property                        | Value                                      |
|--------------------------------|--------------------------------------------|
| PAINS                          | 0 alert                                    |
| Brenk                          | 0 alert                                    |
| Leadlikeness                   | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 |
| Synthetic accessibility        | 4.00                                       |