Facile synthesis of novel tacrine analogues

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The synthesis of highly potent and selective acetylcholinesterase inhibitors, tacrine analogues with the structure of fused 4-aminoquinolines and 4-aminopyridines, has been accomplished by direct cyclocondensation of 1-aryl-4-cyano-5-aminopyrazoles with cyclic ketones using tin(IV) chloride as catalyst.

Keywords: tacrine, pyrazoles, 4-aminoquinolines, 4-aminopyridines, tin(IV) chloride

Alzheimer's disease (AD), the most common form of dementia among the elderly, is a progressive degenerative disorder of the brain with loss of memory and cognition.[1] The social and economic consequences of AD are alarming due to the notable increase in life expectancy. Tacrine is a reversible inhibitor of acetylcholinesterase (AChE) that was launched in 1993 as the first drug for the treatment of AD.[2] In the evaluation of the clinical effects of tacrine, it has shown efficacy in delaying the deterioration of the symptoms of AD, but the poor selectivity of this drug for AChE resulted in a number of side effects, especially hepatotoxicity,[3] and current research is focused on developing new AChE inhibitors with improved activity and reduced adverse side effects. Research has therefore been concentrated on the development of novel tacrine analogues.[4–19]

The main synthetic approach to tacrine analogues is through the cyclocondensation of *o*-aminonitrile derivatives with cyclic ketones using anhydrous $AlCl_3$ as catalyst, but that method leads to yields which are low to moderate. We report here the cyclocondensation of 1-aryl-4-cyano-5-aminopyrazole with cyclic ketones using $SnCl_4$ as catalyst, whereby a series of novel tacrine analogues **3** is generated, in good yields.

Results and discussion

For the investigation of reaction conditions for cyclocondensation of 1-aryl-4- cyano-5-aminopyrazole with cycloketones, we chose the protocol of 1-phenyl-4-cyano-5-aminopyrazole (**1a**) with cyclohexanone as a model reaction. Because the choice of the catalyst played a crucial role, we initially studied the effect of several catalysts on the yields, and we found the use of anhydrous $AlCl_3$, $ZnCl_2$ and $TiCl_4$ was much less effective, and tacrine analogue **3a** was obtained in less than 35% yield, and the product **3a** was not obtained when we used CuCl and $CuCl_2$ as catalysts. When a mixture of 1-phenyl-4-cyano-5-aminopyrazole **1a** and cyclohexanone in toluene was stirred under reflux in the presence of $SnCl_4$, the reaction was completed within 3 h.

Table 1 Effect of the catalyst on the yields[a]

Entry	Catalyst	Yield/%[b]
1	CuCl	0
2	$CuCl_2$	0
3	$AlCl_3$	30
4	$ZnCl_2$	21
5	$TiCl_4$	32
6	$SnCl_4$	82

[a]All reactions were carried out using **1a** (10 mmol), cyclohexanone (10 mmol), catalyst (20 mmol) and toluene (20 mL), refluxing for 3 h.
[b]Isolated yields.

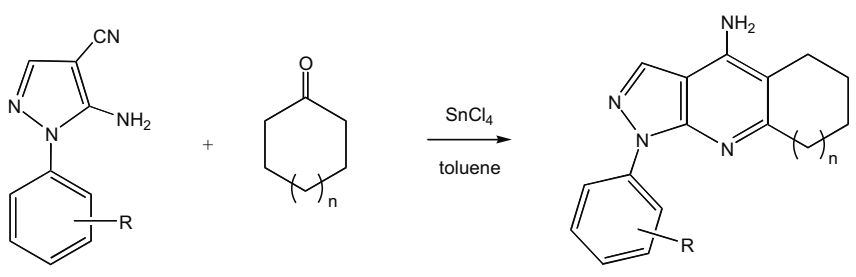
After worked up, the product **3a** was obtained in 82% yield (Table 1). In contrast to the above results, we have found that $SnCl_4$ is the best effective catalyst for the preparation of tacrine analogues **3a**.

In addition, a profound solvent effect on the reaction was observed. We initially studied the effect of non-polar solvents in the reaction, such as DCM, DCE, THF and toluene, in which $SnCl_4$ is easy to dissolve. And then we went on to study the polar solvent DMF. The results are summarised in Table 2. These results suggested that the solvents used have dramatic effects on the yields. Toluene was found to be the best solvent.

Table 2 Effect of the solvent on the yields[a]

Entry	Solvent	Yield/%[b]
1	DCM	56
2	DCE	67
3	THF	53
4	Toluene	82
5	DMF	0

[a]All reactions were carried out using **1a** (10 mmol), cyclohexanone (10 mmol), $SnCl_4$ (20 mmol) and solvent (20 mL), refluxing for 3 h.
[b]Isolated yields.



1 **2** **3**

Scheme 1

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Table 3 Cyclocondensation of 5-amino-1-arylpyrazole-4-carbonitriles and cyclic ketones (Scheme 1)

R	n	Product	Yield/%[a]
H	1	**3a**	82
4-CH_3	1	**3b**	80
3-CH_3	1	**3c**	76
4-Cl	1	**3d**	81
3-Cl	1	**3e**	78
H	0	**3f**	80
4-CH_3	0	**3g**	77
3-CH_3	0	**3h**	73
4-Cl	0	**3i**	79
3-Cl	0	**3j**	75

[a]Isolated yields.

Under the optimised reaction conditions, with $SnCl_4$ as catalyst and anhydrous toluene as solvent, reflux for 3 h, a series of 5-amino-1-arylpyrazole-4-carbonitriles and cyclic ketones were tested and a series of tacrine analogues **3** was thereby prepared in good yields regardless of whether the R group was attached at the 3- or the 4-position in the aryl group. Possibly cyclohexanone is sterically more flexible than cyclopentanone, so the yields of **3a–e** were higher than those of **3f–j** when cyclohexanone was used instead of cyclopentanone for the reaction. The results are summarised in Table 3.

The mechanism of formation of the tacrine analogues **3** can be explained by Scheme 2. The attack of the amino group of **1** onto the carbonyl carbon atom of **2** gave intermediate **4**, and product **3** was obtained through Friedlander reaction.

In conclusion: we have developed an efficient catalyst system for the condensation of pyrazole *o*-aminonitriles with cycloketones using $SnCl_4$ in anhydrous toluene. A facile synthesis of highly potent and selective acetylcholinesterase (AChE) inhibitors, tacrine analogues **3a–j**, was thereby accomplished. In contrast to previous reports, this method requires simple manipulation and provides good yields in short reaction times.

Experimental

All melting points were determined on an XT-4A apparatus. TLC was performed using precoated silica gel GF_{254} (0.25 mm), and column chromatography using silica gel (200–300 mesh). The ^1H and ^{13}C NMR spectra were measured at 25 °C at 300 and 75 MHz, respectively, on a Bruker Avance 300 spectrometer, using TMS as internal standard. *J* values are given in Hz, chemical shifts (δ values) in ppm. The MS spectra were recorded on a Finnigan DECAX-30000 LCQ DecaXP plus instrument. The IR spectra were taken on a Bruker Vector 55 spectrometer. Elemental analyses were obtained using an EA 1112 elemental analyser. 5-Amino-1-arylpyrazole-4-carbonitriles **1** were prepared according to the procedures reported.[20]

Typical procedure

5-Amino-1-phenylpyrazole-4-carbonitrile **1** (10 mmol) and $SnCl_4$ (2.3 mL, 20 mmol) were added to a stirred solution of cyclohexanone or cyclopentanone (10 mmol) in dry toluene (20 mL). The mixture was stirred under nitrogen at room temperature for 30 min and then heated under reflux for 3 h. The reaction mixture was cooled and dispersed into water and adjusted to pH 12–13 with saturated aqueous Na_2CO_3. After filtration, the filtrate was extracted three times with ethyl acetate, the organic layers were dried and evaporated under reduced pressure to give the solid product. The product was purified by silica gel column chromatography eluting with ethyl acetate/petroleum (1:3 v:v) to give **3a–j**.

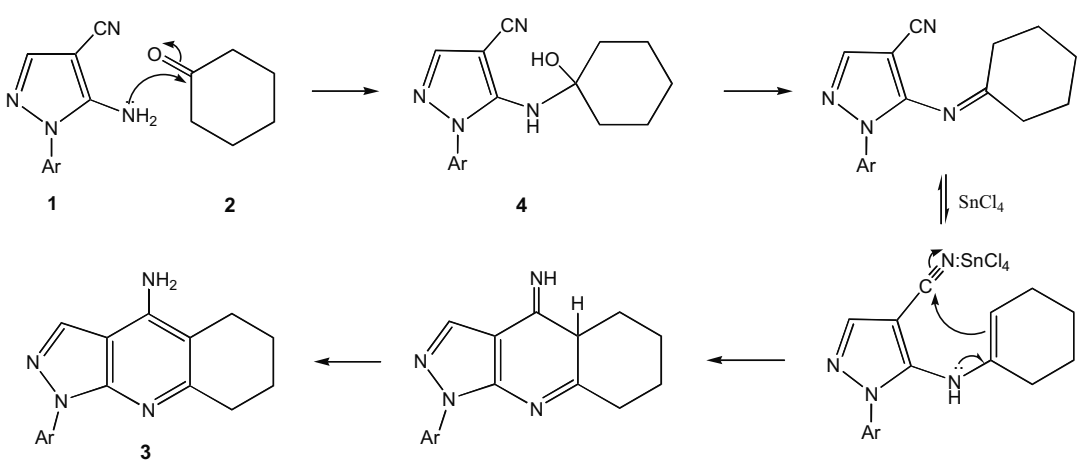
1-Phenyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolin-4-amine (**3a**): Colourless solid; m.p. 186–187 °C. IR (KBr): ν_{max} 3480, 3373, 2934, 2863, 1596, 1490, 1455, 1398, 1350 cm^{-1}. NMR ($CDCl_3$): δ_H 8.29–8.32 (m, 2H), 7.98 (s, 1H), 7.44–7.50 (m, 2H), 7.21–7.26 (m, 1H), 4.60 (br, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.50 (t, *J* = 5.2 Hz, 2H), 1.89 (m, 4H); δ_C 158.5, 150.1, 144.8, 140.1, 130.4, 128.8, 125.2, 120.8, 107.6, 105.5, 34.2, 22.9, 22.8. MS-ESI (*m/z*, relative intensity,%): 266 (M^+ + 3) (1.8), 265 (M^+ + 2) (18), 264 (M^+ + 1) (100). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.91; H, 6.28; N, 21.07%.

1-p-Tolyl-5, 6, 7, 8-tetrahydro-1H-pyrazolo[3, 4-b]quinolin-4-amine (**3b**): Colourless solid; m.p. 177–178 °C. IR (KBr): ν_{max} 3480, 3377, 3250, 2975, 2933, 2864, 1596, 1494, 1453, 1390, 1352 cm^{-1}. NMR ($CDCl_3$): δ_H 8.21 (d, *J* = 8.4 Hz, 2H), 7.98 (s, 1H), 7.29 (m, 2H), 4.55 (br, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.38 (s, 3H), 1.90 (m, 4H); δ_C 158.1, 149.5, 144.4, 137.2, 134.6, 129.6, 129.0, 120.6, 107.0, 104.9, 33.7, 22.5, 22.4, 20.6. MS-ESI (*m/z*, relative intensity,%): 281 (M^+ + 3) (3), 280 (M^+ + 2) (20), 279 (M^+ + 1) (100). Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.54; H, 6.39; N, 19.97%.

1-m-Tolyl-5, 6, 7, 8-tetrahydro-1H-pyrazolo[3, 4-b]quinolin-4-amine (**3c**)**:** Colourless solid; m.p. 171–172 °C. IR (KBr): ν_{max} 3480, 3375, 3246, 2973, 2936, 2862, 1595, 1490, 1457, 1393, 1350 cm^{-1}. NMR ($CDCl_3$): δ_H 8.15 (d, *J* = 8.1 Hz, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 4.56 (br, 2H), 2.98 (t, *J* = 5.1 Hz, 2H), 2.55 (t, *J* = 8.1 Hz, 2H), 2.44 (s, 3H), 1.90 (m, 4H); δ_C 158.4, 149.8, 144.5, 137.8, 134.6, 129.6, 129.5, 125.0, 120.6, 115.6, 107.0, 104.9, 34.0, 22.8, 22.6, 20.9. MS-ESI (*m/z*, relative intensity,%): 302 (7), 301 (32), 299 (M^+ + 1) (100). MS-ESI (*m/z*, relative intensity,%): 281 (M^+ + 3) (4), 280 (M^+ + 2) (21), 279 (M^+ + 1) (100). Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.46; H, 6.72; N, 19.96%.

1-(4-Chlorophenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolin-4-amine (**3d**)**:** Colourless solid; m.p. 189–190 °C. IR (KBr): ν_{max} 3480, 3376, 3248, 2936, 2866, 1596, 1495, 1454, 1398, 1353 cm^{-1}. NMR ($CDCl_3$): δ_H 8.35 (d, *J* = 4.8 Hz, 2H), 7.99 (s, 1H), 7.44 (m, 2H), 4.57 (br, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 1.91 (m, 4H); δ_C 158.7, 150.1, 144.7, 140.8, 130.8, 129.8, 125.0, 120.4, 108.0, 105.5, 34.2, 22.8, 22.7. MS-ESI (*m/z*, relative intensity,%): 302 (7), 301 (31), 299 (M^+ + 1) (100). Anal. Calcd for $C_{16}H_{15}ClN_4$: C, 64.32; H, 5.06; N, 18.75. Found: C, 64.25; H, 5.21; N, 19.20%.

1-(3-Chlorophenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolin-4-amine (**3e**)**:** Colourless solid; m.p. 196–197 cm^{-1}. IR (KBr): ν_{max} 3480, 3376, 3247, 2935, 2864, 1596, 1495, 1454, 1398, 1353 cm^{-1}. NMR ($CDCl_3$): δ_H 8.45 (d, *J* = 2.1 Hz, 1H), 8.33 (m, 1H), 8.00 (s, 1H), 7.39



Scheme 2 Proposed mechanism for tacrine analogue synthesis

(t, J = 8.1 Hz, 1H), 7.18 (m, 1H), 4.58 (br, 2H), 2.99 (t, J = 5.7 Hz, 2H), 2.55 (d, J = 6.0 Hz, 2H), 1.91 (m, 4H); δ_C 158.8, 150.3, 144.8, 141.2, 134.5, 130.8, 129.8, 124.9, 120.4, 118.3, 108.0, 105.6, 34.1, 22.8, 22.7. MS-ESI (*m/z*, relative intensity,%): 302 (6), 301 (30), 299 ($M^+ + 1$) (100). Anal. Calcd for $C_{16}H_{15}ClN_4$: C, 64.32; H, 5.06; N, 18.75. Found: C, 65.13; H, 5.19; N, 18.67%.

1-Phenyl-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[3,4-e]pyridin-4-amine (**3f**)**:** Colourless solid; m.p. 201–202 °C. IR (KBr): ν_{max} 3480, 3375, 3248, 2935, 1591, 1495, 1452, 1398, 1352 cm^{-1}. NMR ($CDCl_3$): δ_H 8.24 (d, J = 7.8 Hz, 2H), 7.99 (s, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.27(m, 1H), 4.53 (br, 2H), 3.06 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.20 (m, 2H); δ_C 167.9, 152.5, 142.6, 139.9, 130.5, 128.9, 125.5, 121.3, 112.3, 105.9, 34.9, 26.3, 23.1. MS-ESI (*m/z*, relative intensity,%): 252 ($M^+ + 3$) (1.5), 251 (17) (18), 250 ($M^+ + 1$) (100). Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 72.20; H, 5.77; N, 22.15%.

1-p-Tolyl-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[3,4-e]pyridin-4-amine (**3g**)**:** Colourless solid; m.p. 268–270 °C. IR (KBr): ν_{max} 3480, 3375, 3246, 2975, 2934, 1590, 1495, 1454, 1397, 1353 m^{-1}. NMR ($CDCl_3$): δ_H 8.10 (d, J = 8.4 Hz, 2H), 8.00 (s, 1H), 7.33 (m, 2H), 4.55 (br, 2H), 3.05 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.38 (s, 3H), 2.20 (m, 2H); δ_C 167.9, 152.5, 142.6, 139.9, 130.5, 128.9, 125.5, 121.3, 112.3, 105.9, 34.9, 26.3, 23.1, 21.1. MS-ESI (*m/z*, relative intensity,%): 267 ($M^+ + 3$) (1.5), 266 ($M^+ + 2$) (18), 265 ($M^+ + 1$) (100). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.53; H, 6.21; N, 21.09%.

1-m-Tolyl-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[3,4-e]pyridin-4-amine (**3h**)**:** Colourless solid; m.p. 225–227 °C. IR (KBr): ν_{max} 3480, 3376, 3241, 2972, 2930, 1596, 1492, 1450, 1396, 1353 cm^{-1}. NMR ($CDCl_3$): δ_H 8.06 (d, J = 6.0 Hz, 2H), 7.99 (s, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 4.50 (br, 2H), 3.07 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.44 (s, 3H), 2.21 (m, 2H); δ_C 167.8, 142.5, 138.7, 131.4, 130.2, 129.5, 128.7, 126.4, 121.9, 118.1, 112.4, 106.7, 34.8, 26.3, 23.1, 21.2. MS-ESI (*m/z*, relative intensity,%): 267 ($M^+ + 3$) (1.5), 266 ($M^+ + 2$) (20), 265 ($M^+ + 1$) (100). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.64; H, 6.22; N, 21.17%.

1-(4-Chlorophenyl)-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[3,4-e]pyridin-4-amine (**3i**): Colourless solid; m.p. 261–263 °C. IR (KBr): ν_{max} 3480, 3375, 3248, 2977, 2936, 1597, 1495, 1453, 1398, 1353 cm^{-1}. NMR ($CDCl_3$): δ_H 8.27 (d, J = 8.8 Hz, 2H), 8.00 (s, 1H), 7.45 (t, J = 9.0 Hz, 2H), 4.51 (br, 2H), 3.03 (t, J = 7.8 Hz, 2H), 2.80 (t, J = 6.9 Hz, 2H), 2.23 (m, 2H); δ_C 167.8, 142.5, 138.7, 134.4, 131.7, 128.7, 126.4, 122.1, 118.1, 112.4, 34.9, 26.3, 23.1. MS-ESI (*m/z*, relative intensity,%): 288 (6), 287 (35), 285 ($M^+ + 1$) (100). Anal. Calcd for $C_{15}H_{13}ClN_4$: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.51; H, 4.75; N, 19.53%.

1-(3-Chlorophenyl)-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[3,4-e]pyridin-4-amine (**3j**): Colourless solid; m.p. 220–222 °C. IR (KBr): ν_{max} 3480, 3377, 3244, 2969, 2931, 1590, 1495, 1451, 1398, 1351 cm^{-1}. NMR ($CDCl_3$): δ_H 8.37 (m, 1H), 8.27 (m, 1H), 8.00 (s, 1H), 7.42 (m, 1H), 7.22(m, 1H), 4.51 (br, 2H), 3.07 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.5 Hz, 2H), 2.22 (m, 2H); δ_C 168.1, 152.6, 142.7, 141.1, 134.5, 130.9, 129.9, 125.3, 120.9, 118.8, 112.9, 106.0, 34.9, 26.3, 23.1. MS-ESI (*m/z*, relative intensity,%): 288 (5), 287 (34), 285 ($M^+ + 1$) (100). Anal. Calcd for $C_{15}H_{13}ClN_4$: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.37; H, 4.74; N, 19.62%.

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