DOI 10.1002/ardp.200500152 Arch. Pharm. Chem. Life Sci. 2005, 338, 590–597

New Pyrimido[5,4-c]cinnolines with Antiplatelet Activities*

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Twenty one new pyrimido[5,4-c]cinnolines containing different lipophilic moieties (viz. phenyl, 4-methoxyphenyl, 2-furanyl, 2-thienyl) in position 2 and additional basic groups (*e.g.*, alkylaminopropyl, dialkylaminopropyl and cyclohexylaminopropyl) in position 4 of the title ring system have been prepared and investigated for antiplatelet effects (Born test). Ten of them inhibited the platelet aggregation induced by collagen with an IC_{50} below 10 μmol/L (**6a**, **6b**, **6c**, **6g**, **6h**, **6i**, **6k**, **6m**, **6q**, **6u**). A closer inspection of the antiplatelet effect with other inducers showed antagonism against adrenaline (**6m**), ADP antagonist (**6i**) and PAF antagonist activities (**6m**, **6i**, **6u**) in nanomolar (IC_{50}) concentration ranges.

Keywords: Pyrimido[5,4-c]cinnolines; Antiplatelet activities; ADP antagonism; Antiadrenergic effects; PAF antagonism

Received: June 6, 2005; Accepted: July 27, 2005

Introduction

In a number of publications [1−3], we have shown that the substitution of heterocycles such as indazoles [1], triazoles [2] or oxadiazoles [3] with a carboxamide partial structure and additional hydrophobic and basic groups leads to a wide variety of compounds with antiplatelet activities at micromolar concentrations. In this paper, we wish to present a number of cinnoline derivatives fulfilling these structural requirements, thus being potential antiplatelet agents.

Pyrimido[5,4-c]cinnolines are a very rare class of compounds. Indeed, only a few studies on this type of compounds have been reported. Gewald [4] synthesized the type **4** with R^1 = H (see Figure 1). On the basis of this synthesis, Menon and Purushotaman [5−7] prepared a number of these compounds and tested them for antibacterial and fungicidal activity. Effects were observed only at high concentrations (100 mM). Nargund *et al.* [8] prepared pyrazolyl derivatives with weak anti-inflammatory potency (250 mg/kg).

Results and discussion

Chemistry

The synthesis of **6** is shown in Figure 1. Aniline (**1**) was converted into benzene diazonium salt, which reacted with cyanoacetamide to **2**. Cyclization with $AlCl_3$ gave the 4-amino cinnoline-3-carboxamide **3**. Reaction with arylcarboxylic acid chlorides gave pyrimido[5,4-c]cinnolines (**4**), which were treated with $POCl_3$ to give the 4-chloro compounds (**5**). Nucleophilic substitution with suitable diamines yielded the completely new type **6** title test compounds.

Biology

The type **6** compounds were assayed in the Born test for their ability to inhibit the aggregation of blood platelets induced by collagen. The results for the most active compounds and a number of substances that further elucidate the structure-activity relationships are summarized in Table 1. Variation of R^1 shows that in all groups studied, compounds with IC_{50} values lower than 10 μM have been found. This is true for R^1 = phenyl (**6a**, **6b**, **6e**), substituted phenyl (**6g**, **6h**, **6i**, **6k**), furyl (**6m**, **6q**) and thienyl (**6u**). Less suitable lipophilic moieties are 4-cyanophenyl, 4-fluorophenyl, and 2-fluorophenyl (IC_{50} = 30−200 μM, data not shown in Table 1), presumably due to the lowered electron density in the aromatic ring compared to the methoxyphenyl group. The antiplatelet effect further depends on sterical factors in R^1. Compounds with space-consuming substituents such as 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl and phenylvinyl show low effects (IC_{50} = 30−300 μM, data not shown in Table 1).

In each R^1-group, the observed antiplatelet effects markedly depend on the R^2 substituent in the 4-amino function. In general, secondary and tertiary amines are potent antiplate-

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* Part of the PhD thesis Hedwig Gonska, FU Berlin, Germany 2004

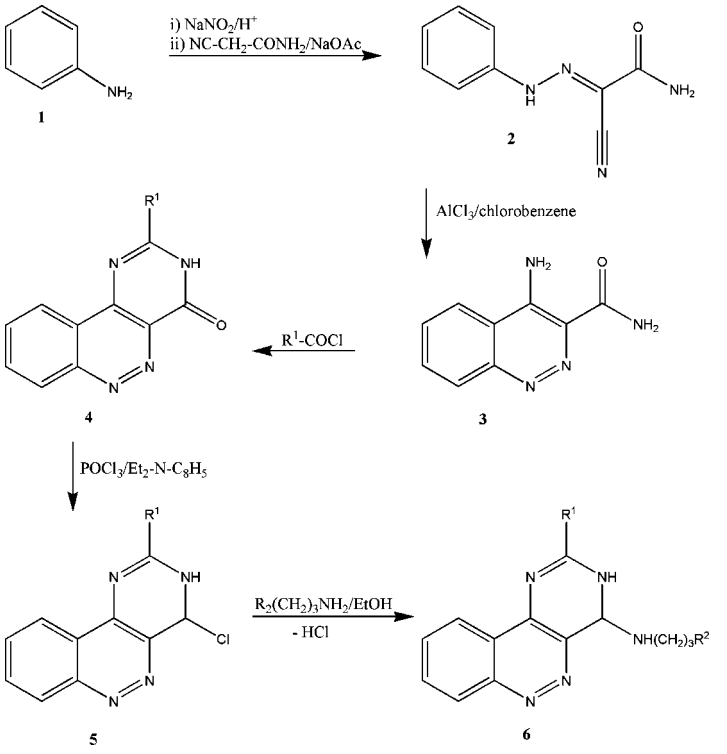

Figure 1. Synthesis of new pyrimido[5,4-c]cinnolines.

Table 1. *In vitro* antiplatelet activities (Born test). IC_{50} values using collagen as inducer are given (incubation time, 20 min). The standard deviation in this test is ≤ 10% (see acetylsalicylic acid, asa).

Compound	R^1	R^2	IC_{50}, μmol/L
6a	phenyl	NH-CH_3	7
6b	phenyl	NH-C_3H_7	9
6c	phenyl	N(C_2H_5)$_2$	7
6d	phenyl	NH-cyclohexyl	48
6e	phenyl	NH-CH-CH_2OH	16
6f	4-methoxyphenyl	N(CH_3)$_2$	71
6g	4-methoxyphenyl	NH-C_3H_7	4
6h	4-methoxyphenyl	N(C_2H_5)$_2$	5
6i	4-methoxyphenyl	NH-cyclohexyl	3
6j	4-methoxyphenyl	NH-CH_2-CH_2-OH	26
6k	2-methoxyphenyl	NH-cyclohexyl	8
6l	4-chlorophenyl	N(C_2H_5)$_2$	96
6m	2-furyl	NH-CH_3	7
6n	2-furyl	NH-C_3H_7	40
6o	2-furyl	N(CH_3)$_2$	15
6p	2-furyl	N(C_2H_5)$_2$	13
6q	2-furyl	NH-cyclohexyl	3
6r	2-furyl	NH-CH_2-OH_2-OH	19
6s	2-thienyl	NH-C_3H_7	19
6t	2-thienyl	N(C_2H_5)$_2$	15
6u	2-thienyl	NH-cyclohexyl	3
6v	2-thienyl	1-imidazolyl	19
asa	–	–	175 ± 20

let compounds (**6a**, **6b**, **6c**, **6g**, **6h**, **6i**, **6m**, **6q**, **6u**). Interestingly, the three most active compounds (**6i**, **6q**, **6u**) all have R^2 = cyclohexylamino combined with R^1 = 4-methoxyphenyl (**6i**), 2-furyl (**6q**) or 2-thienyl (**6u**).

To get an idea concerning the mechanism of action of the antiplatelet compounds, we investigated other inducers than collagen in the Born test. The results are summarized in

Table 2. Inhibition of platelet aggregation induced with ADP, adrenaline or PAF by selected type **6** cinnolines. Incubation time, 20 min. Standard deviation ≤ 10%.

Compound	IC_{50}, μmol/L			
	Adrenaline	ADP	PAF	Collagen
6a	25	15	48	7
6g	17	120	30	4
6h	3	16	40	5
6i	14	**0.8**	**0.8**	3
6m	**0.15**	16	**0.15**	7
6u	7	21	**0.18**	3
Phentolamine mesylate	2	–	–	–
NECA[§]	–	1	–	–
Apafant	–	–	0.6	–
asa	–	–	–	175

§ 5-(N-Ethylcarboxamido)-adenosine

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Table 2. A rather differentiated pattern of effects can be observed. Only compounds **6a** and **6g** are most sensitive against collagen-based platelet aggregation. For **6h** a dual action, *i.e.* on collagen- (IC_{50} = 5 μM) and adrenaline-induced platelet aggregation (IC_{50} = 3 μM), has been shown. With **6m** a strong influence both on the adrenaline- (IC_{50} = 0.15 μM) and PAF-induced (IC_{50} = 0.15 μM) platelet aggregation has been demonstrated, at a far lower concentration than that of the respective standard inhibitors Phentolamine (IC_{50} = 2 μM) and Apafant (IC_{50} = 0.6 μM), respectively. Compound **6i** shows a dual effect directed against ADP- (IC_{50} = 0.8 μM) and PAF-induced (IC_{50} = 0.8 μM) platelet aggregation, which is in the range of the standard inhibitors of NECA or Apafant, respectively. For **6u** a specific antagonism against PAF-induced platelet aggregation (IC_{50} = 0.18 μM) has been observed, which is stronger than that of the standard inhibitor Apafant.

Experimental

General

Mp. (uncorr.), Linström. Elemental analysis: Elementar Vario EL. IR: Perkin Elmer 1420 Ratio Recording IR-Spectrophotometer and ATI Mattson Genesis Serie FTIR. NMR: Bruker Avance/APX 400. EI-MS: CH-7A-Varian MAT (70 eV). The synthesis of **3** has already been reported [4]. All other compounds were prepared for the first time.

General procedure for the synthesis of type 4 (see Fig. 1) pyrimido-[5,4-c]cinnoline-4-ones

Of **3**, 5 mmol suspended in 10 mL pyridine is mixed with a 5−10-fold excess of the acid chloride and stirred for 1−2.5 h at the temperature stated. While cooling with ice, 50 mL water is added. The crystalline precipitate is sucked off and resuspended in 50 mL ethanol/water (1:1). Now, 10 mL NaOH (20%) and 2 mL H_2O_2 (30%) are added. The mixture is kept for 1 h at 90 °C. Mostly at this temperature, a voluminous precipitate of **4** forms, which is sucked off and washed with water and ethanol.

*2-Phenyl-pyrimido[5,4-c]cinnolin-4(3H)-one (**4a**)*

From 1.3 g (6.6 mmol) **3** and 4.3 g (31 mmol) benzoylchloride. 80 °C, 2.5 h. Yellow crystals, mp. > 360 °C (EtOH/H_2O/DMF), yield 1.0 g (61%). Anal. $C_{16}H_{10}N_4O$ (274.3). IR (KBr): ν = 3422 cm^{-1} (NH); 1708 (C=O); 1552; 1499. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.47−7.51 (m, 3H, ph-3,4,5-H), 7.85 (dd, *J* = 7.9/7.0 Hz, 1H, ar-9-H), 7.94 (dd, *J* = 7.6/7.4 Hz, 1H, ar-8-H), 8.53−8.59 (m, 3H, ar-7-H, ph-2,6-H), 8.90 (d, *J* = 8.0 Hz, 1H, ar-10-H). ^{13}C-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 122.44 (C-10a), 123.18 (C-10), 128.16 (ph-C-3,5), 128.71 (ph-2,6-C), 128.95 (ph-C-4), 130.16 (C-8), 130.29 (C-9), 131.01 (C-7), 135.15 (ph-C-1), 139.65 (C-10b), 143.49 (C-6a), 149.14 (C-4a), 165.48 (C-2), 171.30 (C-4). − MS (70 eV): *m/z* (%) = 274 (10) [$M^{+\bullet}$], 105 (100), 77 (35).

*2-(2-Methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-ole (**4b**)*

From 1.1 g (5.5 mmol) **3** and 4.8 g (28 mmol) 2-methoxybenzoylchloride. 60 °C, 2.5 h. Yellow crystals, mp. > 360 °C, yield 0.8 g (47%). Anal. $C_{17}H_{12}N_4O_2$ (304.3). IR (KBr): ν = 3430 cm^{-1} (OH); 1592; 1561; 1508; 1491; 1478; 1378; 1286; 1247; 771. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 3.77 (s, 3H, OCH_3), 7.01 (dd, *J* = 7.6/7.3 Hz, 1H, ph-5-H), 7.09 (d, *J* = 8.2 Hz, 1H, ph-3-H), 7.38 (ddd, *J* = 8.0/7.6/1.8 Hz, 1H, ph-4-H), 7.51 (dd, *J* = 7.4/1.7 Hz, ph-6-H), 7.83 (ddd, *J* = 7.6/6.5/1.0 Hz, 1H, ar-9-H), 7.95 (ddd, *J* = 7.7/7.6/1.2 Hz, ar-8-H), 8.44 (d, *J* = 8.3 Hz, ar-7-H), 8.69 (d, *J* = 7.7 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 304 (14) [$M^{+\bullet}$], 289 (30), 287 (89), 159 (30), 148 (100), 147 (30), 146 (54), 133 (78), 129 (30), 128 (27), 118 (35), 114 (43), 105 (43), 103 (30), 102 (30), 91 (30), 90 (32), 88 (30), 77 (38), 41 (32), 39 (35).

*2-(4-Methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-ole (**4c**)*

From 1.1 g (5.5 mmol) **3** and 4.6 g (27 mmol) 4-methoxybenzoylchloride. 60 °C, 2.5 h. Yellow crystals, mp. > 360 °C, yield 1.1 g (66%). Anal. $C_{17}H_{12}N_4O_2$ (304.3). IR (KBr): ν = 3574 cm^{-1}, 3389 (OH); 3073; 1580; 1559; 1531; 1507; 1482; 1444; 1424; 1403; 1376; 1283; 1250; 1164; 1028; 829; 770; 759. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 3.85 (s, 3H, OCH_3), 7.03 (d, *J* = 8.9 Hz, 2H, ph-3,5-H), 7.85 (ddd, *J* = 7.5/7.5/0.9 Hz, 1H, ar-9-H), 7.94 (ddd, J = 7.7/7.5/1.3 Hz, 1H, ar-8-H), 8.40 (d, *J* = 8.2 Hz, 1H, ar-7-H), 8.54 (d, *J* = 8.8 Hz, 2H, ph-2,6-H), 8.88 (d, *J* = 7.9 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 304 (100) [$M^{+\bullet}$], 303 (27), 276 (12), 275 (11), 143 (10), 134 (32), 133 (16), 119 (21), 115 (15), 103 (13), 91 (10), 90 (14), 63 (10), 44 (18), 41 (14), 39 (13), 31 (12).

*2-(4-Chlorophenyl)-pyrimido[5,4-c]cinnolin-4-ole (**4d**)*

From 1.2 g (6.1 mmol) **3** and 5.6 g (32 mmol) 4-chlorobenzoylchloride. 50 °C, 1.5 h. Yellow crystals, mp. > 360 °C, yield 1.3 g (69%). Anal. $C_{16}H_9ClN_4O$ (308.7). IR (KBr): ν = 3403 cm^{-1} (OH); 1587; 1561; 1533; 1509; 1481; 1392; 1373; 1283; 770. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.56 (dd, *J* = 7.0/1.6 Hz, 2H, ph-3,5-H), 7.90 (ddd, *J* = 7.5/7.4/0.9 Hz, 1H, ar-9-H), 7.99 (ddd, *J* = 8.3/7.0/1.3 Hz, 1H, ar-8-H), 8.46 (d, *J* = 8.2 Hz, 1H, ar-10-H), 8.59 (d, *J* = 8.6 Hz, 2H, ph-2,6-H), 8.91 (d, *J* = 7.6 Hz, 1H, ar-7-H). MS (70 eV): *m/z* (%) = 310 (33) [$M^{+\bullet}$], 309 (26), 308 (100) [$M^{+\bullet}$], 307 (26), 280 (17), 143 (11), 138 (22), 137 (18), 115 (38), 114 (10), 102 (14), 88 (20), 75 (13), 44 (13), 36 (17), 28 (14).

*2-(2-Furyl)-pyrimido[5,4-c]cinnolin-4-ole (**4e**)*

From 1.4 g (7.1 mmol) **3** and 5.4 g (41 mmol) 2-furoylchloride. 60 °C, 2 h. Yellow crystals, mp. > 360 °C, yield 1.5 g (80%). Anal. $C_{14}H_8N_4O_2$ (264.2). IR (KBr): ν = 3401 cm^{-1} (OH); 1602; 1575; 1560; 1531; 1509; 1475; 1451; 1410; 1367; 1370; 1293; 769; 750. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 6.66 (dd, *J* = 3.3/1.6 Hz, 1H, fur-4-H), 7.29 (d, *J* = 3.2 Hz, 1H, fur-5-H), 7.84−7.88 (m, 2H, fur-3H, ar-9H), 7.95 (ddd, *J* = 7.7/7.6/1.3 Hz, 1H, ar-8-H), 8.41 (d, *J* = 8.2 Hz, 1H, ar-10-H), 8.79 (d, *J* = 7.9 Hz, 1H, ar-7-H). MS (70 eV): *m/z* (%) = 264 (1) [$M^{+\bullet}$], 44 (100), 28 (33).

*2-(2-Thienyl)-pyrimido[5,4-c]cinnolin-4-ole (**4f**)*

From 1.1 g (5.5 mmol) **3** and 4.4 g (30 mmol) 2-thienylcarboxylic acid chloride. 60 °C, 2.5 h. Yellow crystals, mp. > 360 °C, yield 1.2 g (78%). Anal. $C_{14}H_8N_4OS$ (280.3). IR (KBr): ν = 3389 cm^{-1} (OH); 1696; 1585; 1561; 1508; 1477; 1430; 1409; 1376; 1338; 1286; 771; 743; 710; 617. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.19 (dd, *J* = 3.9/3.7 Hz, 1H, thi-4-H), 7.67 (d, *J* = 4.5 Hz, 1H, thi-5-H), 7.87 (dd, *J* = 7.3 Hz, 1H, ar-9-H), 7.94−7.99 (m, 2H, ar-8-H, thi-3-H), 8.42 (d, *J* = 8.2 Hz, 1H, ar-10-H), 8.80 (d, *J* = 7.9 Hz, 1H, ar-7-H). MS (70 eV): *m/z* (%) = 280 (100) [$M^{+\bullet}$], 279 (13), 252 (11), 115 (11), 110 (16), 38 (10), 36 (28), 32 (51).

General procedure for the synthesis of type 5 4-chloropyrimido [5,4-c]cinnolines

Of the type **4** pyrimido[5,4-c]cinnoline-4(*3H*)-one or 4-ole, 5 mmol was refluxed with 10 mL $POCl_3$ and 3 mL *N,N*-diethylaniline for the time stated. After cooling to room temperature, the mixture is pored carefully on 200 mL ice water, which is stirred vigorously. The precipitate is sucked off and washed with a small amount of 1 M HCl and finally with ethanol.

*4-Chloro-2-phenyl-pyrimido[5,4-c]cinnoline (**5a**)*

From 0.8 g (2.9 mmol) **4a**, 2.5 h. Light brown crystals, mp. 201 °C, yield 0.6 g (69%). Anal. $C_{16}H_9ClN_4$ (292.7). IR (KBr): ν = 1574 cm^{-1}; 1556; 1529; 1502; 1373; 845; 743; 691. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.63−7.73 (m, 3H, ph-3,4,5-H), 8.26 (ddd, *J* = 7.6/7.4/0.9 Hz, 1H, ar-9-H), 8.33 (ddd, *J* = 8.2/7.6/1.3 Hz, ar-8-H), 8.68−8.71 (m, 2H, ph-2,6-H), 8.87 (d, *J* = 8.0 Hz, 1H, ar-7-H), 9.20 (d, *J* = 7.7 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 294 (34) [$M^{+\bullet}$], 293 (20), 292 (100) [$M^{+\bullet}$], 257 (19) [M^+-Cl], 229 (19), 163 (14), 161 (46), 126 (34), 77 (10).

*4-Chloro-2-(2-methoxyphenyl)-pyrimido[5,4-c]cinnoline (**5b**)*

From 0.8 g (2.6mmol) **4b**, 1 h 45 min. Yellow crystals, mp. 215 °C, yield 0.56 g (65%). Anal. $C_{17}H_{11}ClN_4O$ (322.8). ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 3.92 (s, 3H, OCH_3), 7.19 (dd, *J* = 7.5/7.4 Hz, 1H, ph-5-H), 7.29 (d, *J* = 8.3 Hz, 1H, ph-3-H), 7.60−7.65 (m, 1H, ph-4-H), 7.99 (dd, *J* = 7.6/1.4 Hz, ph-6-H), 8.25 (dd, *J* = 7.4/7.2 Hz, 1H, ar-9-H), 8.33 (dd, *J* = 7.27.0 Hz, ar-8-H), 8.88 (d, J = 8.1 Hz, ar-7-H), 9.05 (d, J = 7.8 Hz, 1H, ar-10-H).

*4-Chloro-2-(4-methoxyphenyl)-pyrido[5,4-c]cinnoline (**5c**)*

From 1.0 g (3.3 mmol) **4c**, 1 h 45 min. Brown crystals, mp. 194 °C (dec.), yield 0.65 g (61%). Anal. $C_{17}H_{11}ClN_4O$ (322.8). IR (KBr): ν = 1606 cm^{-1}; 1573; 1554; 1531; 1517; 1491; 1374; 1259; 1166; 845; 767. ^{1}H-NRM/400 MHz ([D_6]DMSO): δ (ppm) = 3.90 (s, 3H, OCH_3), 7.16 (d, *J* = 8.9 Hz, 2H, 2H, ph-3,5-H), 8.23 (m, 1H, ar-9-H), 8.29 (ddd, *J* = 8.2/7.6/1.2 Hz, 1H, ar-8-H), 8.60 (d, *J* = 8.9 Hz, ph-2,6-H), 8.81 (d, *J* = 8.1 Hz, 1H, ar-7-H), 9.13 (d, *J* = 7.9 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 324 (39) [$M^{+\bullet}$], 323 (21), 322 (100) [$M^{+\bullet}$], 287 (36), 216 (22), 161 (29), 134 (14), 133 (61), 127 (12), 126 (90), 103 (26), 100 (19), 99 (19), 90 (38), 77 (17), 76 (21), 75 (20), 64 (18), 63 (19), 51 (22), 50 (16), 39 (17), 38 (12), 36 (22).

*4-Chloro-2-(4-chlorophenyl)-pyrimido[5,4-c]cinnoline (**5d**)*

From 1.2 g (3.9 mmol) **4d**, 1.5 h. Yellow/green crystals, mp. 221 °C (dec.), yield 0.95 g (74%). Anal. $C_{16}H_8Cl_2N_4$ (327.2). IR (KBr): ν = 1573 cm^{-1}; 1554; 1532; 1400; 1371; 1075; 846; 763. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.73 (d, *J* = 8.6 Hz, 2H, ph-3,5-H), 8.26 (ddd, *J* = 7.6/7.4/0.8 Hz, 1H, ar-9-H), 8.33 (ddd, *J* = 7.7/7.6/1.3 Hz 1H, ar-8-H), 8.69 (d, *J* = 8.6 Hz, 2H, ph-2,6-H), 8.87 (d, *J* = 8.1 Hz, 1H, ar-7-H), 9.20 (d, *J* = 7.8 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 330 (10), 329 (13), 328 (55) [$M^{+\bullet}$], 327 (19), 326 (100) [$M^{+\bullet}$], 291 (13), 263 (15), 228 (11), 163 (21), 161 (61), 126 (44), 100 (13), 75 (15).

*4-Chloro-2-(2-furyl)-pyrimido[5,4-c]cinnoline (**5e**)*

From 1.0 g (3.8 mmol) **4e**, 1 h. Green crystals, mp. 216 °C, yield 0.58 g (54%). Anal. $C_{14}H_7ClN_4O$ (282.7). IR (KBr): ν = 3433 cm^{-1}; 1572; 1552; 1530; 1498; 1471; 1366; 1075; 761. ^{1}H-NMR/400 MHz (D_6]DMSO): δ (ppm) = 6.89 (dd, *J* = 3.5/1.7 Hz, 1H, fur-4-H), 7.76 (d, *J* = 3.5 Hz, 1H, fur-5-H), 8.19−8.24 (m, 2H, fur-3-H, ar-9-H), 8.31 (ddd, *J* = 7.7/7.7/1.2 Hz, 1H, ar-8-H), 8.82 (d, *J* = 8.1 Hz, 1H, ar-7-H), 9.02 (d, *J* = 7.6 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 284 (33) [$M^{+\bullet}$], 283 (15), 282 (100) [$M^{+\bullet}$], 219 (19), 164 (12), 163 (30), 161 (94), 126 (40), 100 (16), 99 (14), 93 (12), 75 (11), 51 (15), 50 (11), 39 (25), 28 (18).

*4-Chloro-2-(2-thienyl)-pyrimido[5,4-c]cinnoline (**5f**)*

From 0.8 g (2.9 mmol) **4f**, 1.5 h. Light brown crystals, mp. 193 °C, yield 0.54 g (62%). Anal. $C_{14}H_7ClN_4S$ (298.7). IR (KBr): ν = 1575 cm^{-1}; 1554; 1536; 1491; 1343; 1406; 1378; 1357; 1075; 831; 780; 761; 729. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 7.37 (dd, *J* = 4.9/3.9 Hz, 1H, thi-4-H), 8,08 (dd, *J* = 5.0/1.0 Hz, 1H, thi-5-H), 8.24 (ddd, *J* = 7.6/7.5/1.1 Hz, 1H, ar-9-H), 8.29−8.33 (m, 2H, Ar-8-H, thi-3-H), 8.83 (d, *J* = 8.1 Hz, 1H, ar-7-H), 9.04 (dd, *J* = 8.0/1.0 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 300 (38) [$M^{+\bullet}$], 299 (16), 298 (100) [$M^{+\bullet}$], 263 (12) [M^+-Cl], 235 (16), 163 (14), 161 (42), 126 (21), 28 (10).

General procedure for the synthesis of the type 6 test compounds

Of the type **5** chlorocinnoline, 1 mmol is dissolved with stirring in 15 mL ethanol and warmed to 60 °C. Of the amine, 10 mmol is slowly added and refluxed for 20 min. After cooling to 4 °C, mostly crystals are formed and sucked off. If no crystals are obtained, the solution is concentrated to 5 mL and dropwise added to 100 mL water. The precipitate is sucked off and washed first with 20 mL ethanol and then with 20 mL water. The compounds are recrystallized from the solvent stated.

*N-Methyl-N′-[(2-phenyl)-pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6a**)*

From 0.30 g (1.02 mmol) **5a** and 1.2 g (16.6 mmol) *N*-methylpropane-1,3-diamine. Light brown crystals, mp. 64 °C (ethanol/ethylacetate), yield 0.24 g (69%). Anal. $C_{20}H_{20}N_6$ (344.4). IR (KBr): ν = 3401 cm^{-1}; 1596; 1577; 1547; 1401; 1376; 1316; 1298; 754; 706. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.94 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.34 (s, 3H, NH-CH_3), 2.65 (t, *J* = 6.6 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.86 (t, *J* = 6.6 Hz, 2H, ar-NH-CH_2), 7.57−7.61 (m, 3H, ph-3,4,5-H), 8.08 (ddd, *J* = 7.6/7.4/0.8 Hz, 1H, ar-9H), 8.14 (ddd, *J* = 7.7/7.5/1.2 Hz, 1H, ar-8-H), 8.64 (d, *J* = 8.2 Hz, 1H, ar-7-H), 8.67−8.69 (m, 2H, ph-2,6-H), 9.01 (d, *J* = 8.0 Hz, 1H, ar-10-H), 9.78 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 344 (11) [$M^{+\bullet}$], 301 (16), 287 (23), 276 (19), 275 (100), 274 (46), 126 (11), 70 (26), 44 (28).

*N-[(2-Phenyl)-pyrimido[5,4-c]cinnolin-4-yl]-N′-propylpropane-1,3-diamine (**6b**)*

From 0.25 g (0.85 mmol) **5a** and 1.2 g (10.3 mmol) *N*-propylpropane-1,3-diamine. Light brown needles, mp. 123 °C (ethanol), yield 0.18 g (56%). Anal. $C_{22}H_{24}N_6$ (372.5). IR (KBr: ν = 3433 cm^{-1}; 1596; 1546; 1546; 1400; 1316; 707. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 0.86 (t, *J* = 7.3 Hz, 1H, NH-CH_2-CH_2-CH_3), 1.39−1.48(m, 2H, NH-CH_2-CH_2-CH_3), 1.93 (tt, *J* = 6.6 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.46−2.48 (m, 2H, NH-CH_2-CH_2-CH_3), 2.69 (t, *J* = 6.5 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.87 (t, *J* = 6.4 Hz, 2H, ar-NH-CH_2), 7.56−7.63 (m, 3H, ph-3,4,5-H), 8.08 (ddd, *J* = 7.6/7.4/1.2 Hz, 1H, ar-9-H), 8.14 (ddd, *J* = 8.2/7.0/1.3 Hz, 1H, ar-8-H), 8.63 (d, *J* = 8.1 Hz, 1H, ar-7H), 8.66−8.70 (m, 2H, ph-2,6-H), 9.02 (dd, *J* = 8.0/0,8 Hz, 1H, ar-10-H), 9.84 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 372 (11) [$M^{+\bullet}$], 301 (18), 300 (11), 287 (17), 276 (19), 275 (100), 274 (32), 98 (39, 30 (16).

*N-[(2-Phenyl)pyrimido[5,4-c]cinnolin-4-yl]-No,No-diethylpropane-1,3-diamine (**6c**)*

From 0.25 g (0.85 mmol) **5a** and 1.8 g (13.8 mmol) *N,N*-diethylpropane-1,3-diamine. Yellow crystals, mp. 88 °C, yield 0.16 g (48%). Anal. $C_{23}H_{26}N_6$ (386.5). IR (KBr): ν = 3356 cm^{-1}; 2969; 1593; 1546; 1398; 1367; 1314; 705. ^{1}H-NMR/400 MHz ([D$_6$]DMSO: δ (ppm) = 1.01 (t, *J* = 7.1 Hz, 6H, 2 × CH_3), 1.95 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.55−2.56 (m, partly overlapped from DMSO, 4H, N-(CH_2-CH_3)$_2$), 2.60−2.61 (br. 2H, ar-NH-CH_2-CH_2-CH_2), 3.82−3.87 (m, 2H, ar-NH-CH_2), 7.56−7.64 (m, 3H, ph-3,4,5-H), 8.07 (ddd, *J* = 7.5/7.5/1.1 Hz, 1H, ar-9-H), 8.14 (ddd, *J* = 7.6/7.5/1.4 Hz, 1H, ar-8-H), 8.65 (d, *J* = 8.3 Hz, 1H, ar-7-H), 8.67−8.69 (m, 2H, ph-2,6-H), 9.01 (dd, *J* = 8.0/0.9 Hz, 1H, ar-10-H), 9.87 (t, *J* = 5.6 Hz, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 386 (11) [$M^{+\bullet}$], 287 (12), 112 (100), 86 (46).

*N-Cyclohexyl-N′-[(2-phenyl)-pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6d**)*

From 0.12 g (0.41 mmol) **5a** and 1.4 g (8.9 mmol) *N*-cyclohexylpropane-1,3-diamine. Light yellow crystals, mp. 131 °C, yield 0.16 g (95%). Anal. $C_{25}H_{28}N_6$ (412.5). IR (KBr): ν = 3360 cm^{-1}; 2927; 2851; 1593; 1576; 1545; 1449; 1397; 1364; 1317; 1299; 707. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.96−1.04 (m, 2H, cyc-3a,5a-H), 1.09−1.23 (m, 3H, cyc-3e,4a,5e-H), 1.50−1.53 (m, 1H, cyc-4e-H), 1.62−1.65 (m, 2H, cyc-2a,6a-H), 1.81−1.84 (m, 2H, cyc-2e,6e-H), 1.91 (tt, *J* = 6.4 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.33−2.38 (m, 1H, cyc-1-H), 2.73 (t, *J* = 6.1 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.88 (br, s, 2H, ar-NH-CH_2), 7.59−7.63 (m, 3H, ph-3,4,5-H), 8.08 (dd, *J* = 7.6/7.4 Hz, 1H, ar-9-H), 8.15 (dd, *J* = 8.2/6.9 Hz, 1H, ar-8-H), 8.65−8.70 (m, 3H, ar-7-H, ph-2,6-H), 9.03 (d, *J* = 8.0 Hz, 1H, ar-10-H), 9.93 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 412 (6) [$M^{+\bullet}$], 287 (12), 276 (16), 275 (100), 274 (19), 138 (57), 56 (18), 30 (15).

*2-[(3-[(2-Phenyl)-pyrimido[5,4-c]cinnolin-4-yl]aminopropyl)-amino]ethanol (**6e**)*

From 0.19 g (0.65 mmol) **5a** and 1.1. g (9.3 mmol) [2-(3-aminopropyl)amino]ethanol. Light green crystals, mp. 198 °C (ethylacetate/DMF), yield 0.14 g (57%). Anal. $C_{21}H_{22}N_6O$ (374.5). IR (KBr): ν = 3412 cm^{-1}; 3342; 1597; 1581; 1547; 1401; 1316. ^{1}H-NMR/400 MHz (D_6]DMSO): δ (ppm) = 1.91−1.97 (tt, *J* = 6.6 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.62 (t, *J* = 5.8 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.74 (t, *J* = 6.6 Hz, NH-CH_2-CH_2-OH), 3.49−3.50 (br, m, 2H, NH-CH_2-CH_2-OH), 3.87−3.89 (m, 2H, ar-NH-CH_2), 4.45 (s, 1H, OH, D_2O exchange), 7.56−7.62 (m, 3H, ph-3,4,5-H), 8.08 (ddd, *J* = 8.0/7.0/1.1 Hz, 1H, ar-9-H), 8.14 (ddd, *J* = 7.7/7.5/1.4 Hz, 1H, ar-8-H), 8.65 (d, *J* = 8.4 Hz, 1H, ar-7-H), 8.67−8.71 (m, 2H, ph-2,6-H), 9.02 (dd, *J* = 8.1/1.1 Hz, 1H, ar-10-H), 9.85 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 374 (10) [$M^{+\bullet}$], 301 (18), 300 (20), 287 (23), 276 (23), 275 (100), 274 (37), 126 (13), 100 (27), 43 (11).

*N-[(2-(4-Methoxyphenyl)pyrimido[5,4-c]cinnolin-4-yl]-N′,N′-dimethylpropane-1,3-diamine (**6f**)*

From 0.20 g (0.62 mmol) **5c** and 1.5 g (14.7 mmol) *N,N*-dimethylpropane-1,3-diamine. Light yellow crystals (ethanol), mp. 172 °C, yield 0.14 g (58%). Anal. $C_{22}H_{24}N_6O$ (3.88.5). IR (KBr): ν = 3476 cm^{-1}; 3423; 1595; 1576; 1547; 1404; 1309; 1253; 1165; 768. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.91 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.22 (s, 6H, 2 × CH_3), 2.45 (t, *J* = 6.8 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.80−3.85 (m, 2H, ar-NH-CH_2), 7.13 (d, *J* = 8.9 Hz, 2H, ph-3,5-H), 8.06 (dd, *J* = 8.0/7.0 Hz, 1H, ar-9-H), 8.11−8.14 (m, 1H, ar-8-H), 8.61−8.65 (m, 1H, ph-2,6-H, ar-7-H), 9.00 (d, *J* = 7.8 Hz, 1H, ar-10-H), 9.67 (t, *J* = 5.7 Hz, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 388 (3) [$M^{+\bullet}$], 317 (19), 304 (28), 85 (16), 84 (100), 58 (61), 32 (34), 28 (99).

*N-[2-(4-Methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-yl]-N′-propylpropane-1,3-diamine (**6g**)*

From 0.20 g (0.62 mmol) **5c** and 1.2 g (10.3 mmol) *N*-propylpropane-1,3-diamine. Light brown needles, mp. 83 °C, yield 0.22 g (87%). Anal. $C_{23}H_{26}N_6O$ (402.5). IR (KBr): ν = 1593 cm^{-1}; 1575; 1546; 1402; 1308; 1251; 1164; 769. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.86 (t, *J* = 7.4 Hz, 3H, NH-CH_2-CH_2-CH_3), 1.39−1.48 (m, 2H, NH-CH_2-CH_2-CH_3), 1.92 (tt, *J* = 6.5 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.47 (t, partly overlapped by DMSO, J = 7.1 Hz, 2H, NH-CH_2-CH_2-CH_3), 2.69 (t, *J* = 6.4 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.86−3.88 (m, 5H, ar-NH-CH_2, OCH_3), 7.12 (d, *J* = 8.8 Hz, 2H, ph-3,5-H), 8.06 (dd, *J* = 7.6/7.2 Hz, 1H, ar-9-H), 8.12 (dd, *J* = 7.3/7.1 Hz, 1H, ar-8-H), 8.61−8.64 (m, 3H, ar-7-H, ph-2,6-H), 8.99 (d, *J* = 8.0 Hz, 1H, ar-10-H), 9.76 (br, s, 1H, ar-NH, D_2O exchange). MS (EI, 70 °C): *m/z* (%) = 402 (14) [$M^{+\bullet}$], 331 (13), 317 (18), 306 (20), 305 (100), 304 (38), 126 (11), 98 (30), 30 (17), 28 (16).

*N,N-Diethyl-No-[(2-(4-methoxyphenyl)pyrimido[5,4-c]cinnolin-4-yl)propane-1,3-diamine-semihydrate (**6h**)*

From 0.25 g (0.77 mmol) **5c** and 1.7 g (13.1 mmol) *N,N*-diethylpropane-1,3-diamine. Yellow crystals, mp. 138 °C, yield 0.19 g (59%). Anal. $C_{24}H_{28}N_6O$ ± 0.5 H_2O (425.5). IR (KBr): ν = 3438 cm^{-1}; 3339; 1599; 1576, 1547; 103; 1308; 1257; 1166; ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.00 (t, *J* = 7.0 Hz, 6H, 2 × CH_3), 1.92 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.53−2.55 (partly overlapped by the DMSO peak, m, 4H, N-(CH_2-CH_3)$_2$), 2.59 (t, *J* = 6.6 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.81−3.86 (m, 2H, ar-NH-CH_2), 3.88 (s, 3H, OCH_3), 7.11 (d, *J* = 8.8 Hz, 2H, ph-3,5-H), 8.04−8.08 (m, 1H, ar-9H), 8.13 (ddd, *J* = 7.3/7.1/1.2 Hz, 1H, ar-8-H), 8.61−8.65 (m, 3H, ar-7-H, ph-2,6-H), 8.99 (d, *J* = 7.9 Hz, 1H, ar-10-H), 9.77 (t, *J* = 5.5 Hz, 1H, ar-NH, D_2O exchange). (CF_3COOD): δ (ppm) = 1.49 (t, *J* = 7.3 Hz, 6H, 2 × CH_3), 2.60−2.64 (m, 2H, ar-NH-CH_2-CH_2-CH_2), 3.41−3.52 (m, 4H, N-(CH_2-CH_3)$_2$), 3.58−3.62 (m, 2H, ar-NH-CH_2-CH_2-CH_2), 4.11 (s, 3H, OCH_3), 4.40 (t, *J* = 7.0 Hz, 2H, ar-NH-CH_2), 7.32 (d, *J* = 9.1 Hz, 2H, ph-3,5-H), 8.54−8.57 (m, 3H, ar-9-H, ph-2,6-H), 8.67 (dd, *J* = 8.2/7.7 Hz, 1H, ar-8-H), 8.89 (d, *J* = 8.7 Hz, 1H, ar-7-H), 9.28 (d, *J* = 8.6 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 416 (15) [$M^{+\bullet}$], 317 (12), 304 (10), 113 (10), 112 (100), 86 (41), 28 (13).

*N-Cyclohexyl-N′-[2-(4-Methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6i**)*

From 0.40 g (1.24 mmol) **5c** and 2.5 g (15.9 mmol) *N*-cyclohexylpropane-1,3-diamine. Yellow crystals, mp. 155 °C, yield 0.31 g (56%). Anal. $C_{26}H_{30}N_6O$ (442.6). IR (KBr). ν = 2927 cm^{-1}; 1595; 1575; 1546, 1403; 1375; 1309; 1251; 1164; 769. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.96−1.08 (m,, 2H, cyc-3a,5a-H), 1.09−1.22 (m, 3H, cyc-3e,4a,5e-H), 1.51−1.53 (m, 1H, cyc-4e-H), 1.62−1.65 (m, 2H, cyc-2a,6a-H), 1.90 (tt, *J* = 6.5 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.33−2.39 (m, 1H, cyc-1H), 2.73 (t, *J* = 6.4 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.85−3.89 (m, 5H, ar-NH-CH_2, OCH_3), 7.12 (d, *J* = 8.9 Hz, 2H, ph-3,5-H), 8.06 (ddd, *J* = 7.6/7.4/0.8 Hz, 1H, ar-9-H), 8.12 (ddd, *J* = 7.7/7.5/1.3 Hz, 1H, ar-8-H), 8.62−8.64 (m, 3H, ar-7-H, ph-2,6-H), 8.99 (dd, *J* = 7.6/0.9 Hz, 1H, ar-10-H), 9.82 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 442 (9) [$M^{+\bullet}$], 317 (13), 306 (21), 305 (100), 304 (25), 138 (37), 56 (20), 30 (18), 28 (33).

*2-[(3-[(2-(4-Methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-yl]amino-propyl)amino]ethanol (**6j**)*

From 0.25 g (0.77 mmol) **5c** and 1.3 g (6.9 mmol) [2-(3-aminopropyl)amino]ethanol. Yellow crystals (ethanol/ethylacetate), mp. 145 °C, yield 0.21 g (68%). Anal. $C_{22}H_{24}N_6O_2$ (404.5). IR (KBr): ν = 3345 cm^{-1}; 1595; 1576; 1546; 1437; 1403; 1378; 1251; 1164; 767. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.94 (tt, *J* = 6.6. Hz, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 2.62 (t, *J* = 5.8 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 2.73 (t, *J* = 6.5 Hz, NH-CH$_2$-CH$_2$-OH), 3.49 (br, m, 2H, NH-CH$_2$-C*H*$_2$-OH), 3.85–3.86 (m, 2H, ar-NH-C*H*$_2$), 3.88 (s, 3H, OCH$_3$), 4.45 (s, 1H, OH, D$_2$O exchange), 7.12 (d, 2H, ph-3,5-H), 8.06 (dd, *J* = 7.2/7.0 Hz, 1H, ar-9-H), 8.12 (ddd, *J* = 7.7/7.5/1.2 Hz, 1H, ar-8-H), 8.61–8.65 (m, 3H, ar-7-H, ph-2,6-H), 8.99 (d, *J* = 7.4 Hz, 1H, ar-10-H), 9.75 (s, 1H, ar-NH, D$_2$O exchange). MS (70 eV): *m/z* (%) = 404 (14) [M$^{+\bullet}$], 331 (14), 330 (21), 319 (23), 318 (11), 309 (20), 307 (100), 306 (45), 127 (13), 126 (20), 100 (27), 56 (11), 45 (10), 44 (14), 31 (15), 30 (14).

*N-Cyclohexyl-N′-[2-(2-methoxyphenyl)-pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6k**)*

From 0.20 g (0.62 mmol) **5b** and 1.9 g (12.1 mmol) *N*-cyclohexylpropane-1,3-diamine. Light yellow crystals, mp. 100 °C, yield 0.18 g (66%). Anal. $C_{26}H_{30}N_6O$ (442.6). IR (KBr): ν = 3415 cm^{-1}; 3338; 2924; 1597; 1546; 1301. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.89–0.97 (m, 2H, cyc-3a,5a-H), 1.04–1.18 (m, 3H, cyc-3e,4a,5e-H), 1.49–1.52 (m, 1H, cyc-4e-H), 1.59–1.62 (m, 2H, cyc-2a,6a-H), 1.74–1.77 (m, 1H, cyc-2e,6e-H), 1.87 (tt, *J* = 6.5 Hz, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 2.28–2.33 (m, 1H, cyc-1-H), 2.66 (t, *J* = 6.3 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 3.73–3.75 (m, 2H, ar-NH-C*H*$_2$), 3.85 (s, 3H, OCH$_3$), 7.09 (dd, *J* = 7.5/7.2 Hz, 1H, ph-4-H), 7.20 (d, *J* = 8.3 Hz, 1H, ph-3-H), 7.50 (ddd, *J* = 7.9/7.6/1.8 Hz, 1H, ph-5-H), 7.80 (dd, *J* = 7.6/1.8 Hz, 1H, ph-6-H), 8.04 (dd, *J* = 8.0/7.1 Hz, 1H, ar-9-H), 8.13 (ddd, *J* = 7.6/7.6/1.3 Hz, 1H, ar-8-H), 8.66 (d, *J* = 8.2 Hz, 1H, ar-7-H), 8.84 (d, *J* = 8.0 Hz, 1H, ar-10-H), 9.83 (s, 1H, ar-NH, D$_2$O exchange). MS (70 eV): *m/z* (%) = 442 (3) [M$^{+\bullet}$], 317 (11), 306 (20), 305 (100), 304 (19), 138 (19), 56 (12), 30 (11).

*N-[(2-(4-Chlorophenyl)pyrimido[5,4-c]cinnolin-4-yl]-N′,N′-diethylpropane-1,3-diamine (**6l**)*

From 0.3 g (0.92 mmol) **5d** and 1.7 g (13.1 mmol) *N,N*-diethylpropane-1,3-diamine. Yellow crystals, mp. 127 °C, yield 0.24 g (62%). Anal. $C_{23}H_{25}ClN_6$ (420.9). IR (KBr): ν = 3431 cm^{-1}; 1600; 1576; 1547; 1400; 1310. ^{1}H-NMR/400 MHz (CF$_3$COOD): δ (ppm) = 1.48 (t, *J* = 7.3 Hz, 6H, 2 × CH$_3$), 2.58–2.66 (m, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 3.39–3.53 (m, 4H, N-(C*H*$_2$-CH$_3$)$_2$), 3.58–3.62 (m, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 4.42 (t, *J* = 6.9 Hz, 2H, ar-NH-C*H*$_2$), 7.78 (d, *J* = 8.6 Hz, 2H, ph-3,5-H), 8.45 (d, *J* = 8.6 Hz, 2H, ph-2,6-H), 8.55 (dd, *J* = 8.0/7.6 Hz, 1H, ar-9-H), 8.65 (dd, *J* = 8.2/7.5 Hz, 1H, ar-8-H), 8.95 (d, *J* = 8.6 Hz, 1H, ar-7-H), 9.27 (d, *J* = 8.6 Hz, 1H, ar-10-H). MS (70 eV): *m/z* (%) = 420 (7) [M$^{+\bullet}$], 112 (100), 86 (53), 30 (10).

*N-[2-(2-Furyl)pyrimido[5,4-c]cinnolin-4-yl]-N′-methylpropane-1,3-diamine (**6m**)*

From 0.21 g (0.74 mmol) **5e** and 1.3 g (18.0 mmol) *N*-methylpropane-1,3-diamine. Slightly brown crystals, mp. 119 °C (ethanol/ethylacetate), yield 0.14 g (57%). Anal. $C_{18}H_{18}N_6O$ (334.4). IR (KBr): 3343 cm^{-1}; 3297; 1605; 1576; 1545; 1480; 1431; 1365; 1316; 767. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.89 (tt, *J* = 6.7 Hz, 2H, NH-CH$_2$-C*H*$_2$-CH$_2$), 2.29 (s, 3H, NH-CH$_3$), 2.61 (t, J = 6.5 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 3.79 (t, *J* = 6.6 Hz, 2H, ar-NH-CH$_2$), 6.77 (dd, *J* = 3.2/1.6 Hz, 1H, fur-4-H), 7.54 (d, *J* = 3.3 Hz, 1H, fur-5-H); 8.03–8.08 (m, 2H, fur-3-H, ar-9-H), 8.13 (dd, *J* = 8.3/7.0 Hz, ar-8-H), 8.62 (d, *J* = 8.2 Hz, 1H, ar-7-H), 8.88 (d, *J* = 7.9 Hz, 1H, ar-10-H), 9.75 (s, 1H, ar-NH, D$_2$O exchange). MS (EI; 70 °C): *m/z* (%) = 334 (13) [M$^{+\bullet}$], 291 (16), 277 (22), 266 (19), 265 (100), 264 (47), 107 (35), 71 (20), 70 (39), 69 (16), 57 (23), 55 (11), 44 (29), 43 (26), 42 (10), 41 (14).

*N-[2-(2-Furyl)pyrimido[5,4-c]cinnolin-4-yl]-N′-propylpropane-1,3-diamine (**6n**)*

From 0.25 g (0.88 mmol) **5e** and 1.4 g (12.1 mmol) *N*-propylpropane-1,3-diamine. Yellow crystals, mp. 118 °C (ethanol), yield 0.15 g (47%). Anal. $C_{20}H_{22}N_6O$ (362.4). IR (KBr): 3351 cm^{-1}; 2954; 2954; 2931; 2872; 1602; 1574; 1544; 1480; 1432; 1403; 1365; 1318; 1239; 1009; 779; 766; 743. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.86 (t, *J* = 7.4 Hz, 3H, NH-CH$_2$-CH$_2$-C*H*$_3$), 1.39–1.48 (m, 2H, NH-CH$_2$-C*H*$_2$-CH$_3$), 1.89 (tt, *J* = 6.5 Hz, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 2.47 (t, *J* = 7.1 Hz, 2H, NH-C*H*$_2$-CH$_2$-CH$_2$), 2.66 (t, J = 6.4 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 3.80 (t, *J* = 6.4 Hz, 2H, ar-NH-C*H*$_2$), 6.78 (dd, J = 3.2/1.6 Hz, 1H, fur-4-H), 7.53 (dd, *J* = 3.3 Hz, 1H, fur-5-H), 8.03–8.07 (m, 2H, fur-3-H, ar-9-H), 8.11–8.14 (m, 1H, ar-8-H), 8.62 (d, *J* = 8.2 Hz, 1H, ar-7-H), 8.88 (d, *J* = 7.9 Hz, 1H, ar-10-H), 9.81 (s, 1H, ar-NH, D$_2$O exchange). MS (70 eV): *m/z* (%) = 362 (7) [M$^{+\bullet}$]. 291 (13), 290 (10), 277 (17), 266 (16), 265 (100), 126 (11), 98 (75), 72 (16), 70 (11), 56 (13), 44 (14), 43 (22), 42 (11), 41 (18), 39 (12), 20 (68), 28 (18), 27 (12).

*N-[2-(2-Furyl)pyrimido[5,4-c]cinnolin-4-yl]-N′,N′-dimethylpropane-1,3-diamine (**6o**)*

From 0.30 g (1.06 mmol) **5e** and 1.3 g (12.8 mmol) *N,N*-dimethylpropane-1,3-diamine. Green crystals, mp. 119 °C, yield 0.22 g (57%). Anal. $C_{19}H_{20}N_6O$ (348.4). IR (KBr): 3341 cm^{-1}; 1606; 1574; 1544; 1495; 1479; 1436; 1367; 1316; 1265; 1241; 764. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.91 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 2.20 (s, 6H, 2 × CH$_3$), 2.39 (t, *J* = 6.8 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 3.74–3.79 (m, 2H, ar-NH-C*H*$_2$), 6.77 (dd, J = 3.4/1.6 Hz, 1H, fur-4-H), 7.52 (d, *J* = 3.5 Hz, 1H fur-5-H), 8.03–8.07 (m, 2H, fur-3-H, ar-9-H), 8.13 (ddd, *J* = 8.2/7.0/1.3 Hz, 1H, ar-8-H), 8.62 (d, *J* = 7.6 Hz, 1H, ar-7-H), 8.87–8.90 (m, 1H, ar-10-H), 9.71 (t, *J* = 5.7 Hz, ar-NH, D$_2$O exchange). MS (70 eV): *m/z* (%) = 348 (3) [M$^{+\bullet}$], 277 (21), 264 (22), 85 (16), 84 (100), 58 (61).

*N,N-Diethyl-N′-[2-(2-furyl)pyrimido[5,4-c]cinnolin-4-yl]-1,3-propanediamine (**6p**)*

From 0.30 g (1.06 mmol) **5e** and 1.7 g (13.1 mmol) *N,N*-diethylpropane-1,3-diamine. Yellow green crystals (ethylacetate), mp. 93 °C, yield 0.21 g (51%). Anal. $C_{21}H_{24}N_6O$ (376.5). IR (KBr): ν = 3340 cm^{-1}; 2969; 2796; 1603; 1575; 1545; 1497; 1480; 1433; 1368; 1318; 1241; 1012; 763. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.00 (t, J = 7.1 Hz, 6H, 2 × CH$_3$), 1.90 (tt, *J* = 6.7 Hz, 2H, ar-NH-CH$_2$-C*H*$_2$-CH$_2$), 2.53–2.55 (overlapped by DMSO peak, m, 4H, N-(CH$_2$-CH$_3$)$_2$), 2.59 (t, *J* = 6.6 Hz, 2H, ar-NH-CH$_2$-CH$_2$-C*H*$_2$), 3.78 (t, *J* = 6.4 Hz, 2H, ar-NH-C*H*$_2$), 6.77(dd, *J* = 3.3/1.7 Hz, 1H, fur-4-H), 7.52 (d, *J* = 3.1 Hz, 1H, fur-5-H), 8.02–8.07 (m, 2H, fur-3-H, ar-9-H), 8.11–8.15 (m, 1H, ar-8-H), 8.63 (d, *J* = 8.3 Hz, 1H, ar-7-H), 8.88 (dd, *J* = 8.0/1.0 Hz, 1H, ar-10-H), 9.85 (t, *J* = 5.5 Hz, ar-NH, D$_2$O exchange). MS (70 eV): *m/z* (%) = 376 (13) [M$^{+\bullet}$], 277 (14), 112 (100), 86 (44).

*N-Cyclohexyl-N′-[2-(2-furyl)pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6q**)*

From 0.28 g (0.99 mmol) **5e** and 1.3 g (8.3 mmol) *N*-cyclohexylpropane-1,3-diamine. Ochroid small crystals, mp. 118 °C, yield 0.38 g

(95%). Anal. $C_{23}H_{26}N_6O$ (402.5). IR (KBr): ν = 2926 cm^{-1}; 1605; 1575; 1545; 1480; 1366; 1315; 766. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.96−1.22 (m, 5H, cyc-3a,3e,4a,5a,5e-H), 1.51−1.53 (m, 1H, cyc-4e-H), 1.62−1.65 (m, 2H, cyc-2a,5a-H), 1.81−1.90 (m, 4H, cyc-2e,6e-H, ar-NH-CH_2-CH_2-CH_2), 2.32−2.37 (m, 1H, cyc-1-H), 2.68−2.71 (m, 2H, ar-NH-CH_2-CH_2-CH_2), 3.80 (s. broad, 2H, ar-NH-CH_2), 6.77 (dd, *J* = 3.2/15 Hz, 1H, fur-4-H), 7.53 (d, *J* = 3.2 Hz, 1H, fur-5-H), 8.03−8.15 (m, 2H, fur-3-H, ar-9-H), 8.13 (dd, *J* = 7.9/7.2 Hz, 1H, ar-8-H), 8.63 (d, *J* = 8.3 Hz, 1H, ar-7-H), 8.88 (d, *J* = 7.9 Hz, 1H, ar-10-H), 9.89 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 402 (5) [$M^{+\bullet}$], 277 (14), 266 (16), 265 (100), 56 (21), 30 (14).

*2-[(3-[(2-Furyl)pyrimido[5,4-c]cinnnolin-4-yl]aminopropyl)-amino]ethanol (**6r**)*

From 0.30 g (1.06 mmol) **5e** and 1.7 g (14.4 mmol) [2-(3-aminopropyl)amino]ethanol. Light green crystals, mp. 183 °C (ethanol/H_2O/DMF), yield 0.13 g (36%). Anal. $C_{19}H_{20}N_6O_2$ (364.4). IR (KBr): ν = 3343 cm^{-1}; 3311; 2830; 1603; 1574; 1544; 1496, 1476; 1434; 1405; 1367; 1315; 1241; 765. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.90 (tt, J = 5.5 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.61 (t, *J* = 5.8 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.70 (t, *J* = 6.5 Hz, 2H, NH-CH_2-CH_2-OH), 3.48−3.51 (br. m, 2H, NH-CH_2-CH_2-OH), 3.79 (br, m, 2H, ar-NH-CH_2), 4.45 (s, 1H, OH, D_2O exchange), 6.76−6.78 (m, 1H, fur-4-H), 7.54 (d, *J* = 3.5 Hz, 1H, fur-5-H), 8.02−8.08 (m, 2H, fur-3-H, ar-9-H), 8.11−8.15 (m, 1H, ar-8-H), 8.62 (d, *J* = 8.1, 1H, ar-7-H), 8.87 (d, J = 7.7 Hz, 1H, ar-10-H), 9.84 (s, 1H, ar-NH, D_2O exchange). MS (EI, 70 °C): *m/z* (%) = 364 (11) [$M^{+\bullet}$], 291 (21), 290 (28), 277 (22), 276 (11), 266 (18), 265 (100), 264 (47), 263 (11), 126 (13), 100 (30), 56 (11).

*N-Propyl-N′-[2-(2-thienyl)pyrimido[5,4-c]cinnolin-4-yl]propane-1,3-diamine (**6s**)*

From 0.30 g (1.00 mmol) **5f** and 1.5 g (12.9 mmol) *N*-propylpropane-1,3-diamine. Light brown crystals, mp. 134 °C (ethanol/ethylacetate), yield 0.26 g (69%). Anal. $C_{20}H_{22}N_6S$ (378.5). IR (KBr): ν = 3351 cm^{-1}; 1595; 1575; 1537; 1524; 1433; 1311; 765. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.86 (t, *J* = 7.4 Hz, 3H, NH-CH_2-CH_2-CH_3), 1.39−1.48 (m, 2H, NH-CH_2-CH_2-CH_3), 1.90 (tt, *J* = 6.6 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.47 (partly overlapped by DMSO peak, m, 2H, NH-CH_2-CH_2-CH_3), 2.68 (t, *J* = 6.5 Hz, 2H, ar-CH_2-CH_2-CH_2), 3.80 (d, *J* = 6.5 Hz, 2H, ar-NH-CH_2), 7.28 (dd, *J* = 4.8/3.9 Hz, 1H, thi-4-H), 7.87 (dd, *J* = 5.0/0.8 Hz, 1H, thi-5-H), 8.06 (dd, *J* = 7.1/7.0 Hz, 1H, ar-9-H), 8.11−8.15 (m, 1H, ar-8-H), 8.17 (dd, *J* = 3.5/0.9 Hz, 1H, thi-3-H), 8.62 (d, *J* = 8.1 Hz, 1H, ar-7-H), 8.87−8.89 (m, 1H, ar-10-H), 9.84 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 378 (11) [$M^{+\bullet}$], 361 (25), 360 (13); 322 (25), 321 (12), 320 (34), 319 (18), 307 (20), 306 (20), 293 (25), 292 (21), 282 (17), 281 (100), 155 (11), 135 (11), 127 (15), 126 (25), 110 (10), 98 (57), 72 (11), 43 (14), 41 (13), 30 (26), 28 (37).

*N′,N′-Diethyl-N-[2-(2-thienyl)pyrimido[5,4-c]cinnolin-4-yl]-propane-2,3-diamine (**6t**)*

From 0.30 g (1.00 mmol) **5f** and 1.3 g (10.0 mmol) *N,N*-diethylpropane-1,3-diamine. Light green crystals, mp. 91 °C, yield 0.35 g (89%). Anal. $C_{21}H_{24}N_6S$ (392.5). IR (KBr): ν = 3351 cm^{-1}; 2967; 1595; 1577; 1536; 1524; 1433; 1392; 1367; 1343; 1308; 763; 706. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.00 (t, J = 7.1 Hz, 6H, 2 × CH_3), 1.90 (tt, J = 6.8 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.52 (overlapped by DMSO peak, m, 4H, N-(CH_2-CH_3)$_2$), 2.59 (t, *J* = 6.7 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 3.76−3.81 (m, 2H, ar-NH-CH_2), 7.28 (dd, J = 4.9/3.8 Hz, 1H, thi-4-H), 7.87 (dd, *J* = 4.9/1.1 Hz, 1H, thi-5-H), 8.04−8.08 (m, 1H, ar-9-H), 8.13 (ddd, *J* = 3.7/1.1 Hz, thi-3-H), 8.63 (d, *J* = 8.1 Hz, 1H, ar-7-H), 8.87−8.89 (m, 1H, ar-10-H), 9.87 (t, *J* = 5.6 Hz, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 392 (9) [$M^{+\bullet}$], 112 (100), 86 (86), 72 (18), 58 (48), 56 (31), 44 (17), 43 (16), 42 (38), 41 (14), 39 (12), 30 (80), 29 (45), 28 (28), 27 (11).

*N-Cyclohexyl-N′-[2-(2-thienyl)pyrimido[5,4-c]cinnolin-4-yl]-propane-1,3-diamine (**6u**)*

From 0.30 g (1.00 mmol) **5f** and 1.3 g (8.3 mmol) N-cyclohexylpropane-1,3-diamine. Yellow green crystals, mp. 124 °C, yield 0.22 g (52%). Anal. $C_{23}H_{26}N_6S$ (418.6). IR (KBr): ν = 3350 cm^{-1}; 2926; 2851; 1593; 1576; 1536; 1524; 1432; 1392; 1366; 1343; 1311; 464; 706. ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.96−1.22 (m, 5H, cyc-3a,3e,4a,5a,5e-H), 1.51−1.53 (m, 1H, cyc-4e-H), 1.62−1.66 (m, 2H, cyc-2a,6a-H), 181−1.85 (m, 2H, cyc-2e,6e-H), 1.90 (tt, *J* = 6.4 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 2.33−2.39 (m, 1H, cyc-1-H), 2.70−2.73 (m, 2H, ar-NH-CH_2-CH_2-CH_2), 3.80 (br, s, 2H, ar-NH-CH_2), 4.37 (s, 1H, cyc-NH, partly exchanged), 7.27 (dd, *J* = 4.9/3.7 Hz, 1H, thi-4-H), 7.87 (dd, *J* = 5.0/0.9 Hz, 1H, thi-5-H), 8.06 (dd, *J* = 7.1/6.8 Hz, 1H, ar-9-H), 8.13 (ddd, *J* = 7.7/7.5/1.3 Hz, 1H, ar-8-H), 8.16−8.17 (m, 1H, thi-3-H), 8.62 (d, *J* = 8.1 Hz, 1H, ar-7-H), 8.68 (d, *J* = 7.5 Hz, 1H, ar-10-H)), 9.91 (s, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 418 (7) [$M^{+\bullet}$], 307 (12), 293 (16), 282 (20), 281 (100), 280 (23), 138 (78), 56 (21), 30 (15).

*N-[3-(1H-Imidazol-1-yl)propyl]-2-(2-thienyl)-pyrimido[5,4-c]-cinnolin-4-amine (**6v**)*

From 0.25 g (0.83 mmol) **5f** and 2.2 g (17.6 mmol) 3-(1-imidazolyl)-propylamine. Light brown crystals, mp. 177 °C, yield 0.11 g (34%). Anal. $C_{20}H_{17}N_7S$ (387.5). IR (KBr) ν = 3347 cm^{-1} (NH); 1595; 1577; 1536; 1524; 1433; 1393; 1370; 1313; 764; 726. ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.20−2.27 (m, 2H, ar-NH-CH_2-CH_2-CH_2), 3.71−3.76 (m, 2H, ar-NH-CH_2), 4.15 (t, *J* = 6.8 Hz, 2H, ar-NH-CH_2-CH_2-CH_2), 6.91 (s, 1H, im-5-H), 7.26 (s, 1H, im-4-H), 7.28 (dd, *J* = 4.9/3.8 Hz, 1H, thi-4-H), 7.70 (s, 1H, im-2-H), 7.87 (dd, *J* = 4.8/0.9 Hz, 1H, thi-5-H), 8.07 (m, 1H, ar-9-H), 8.11−8.15 (m, 2H, ar-8-H, thi-3-H), 8.63 (d, *J* = 8.1 Hz, ar-7-H), 8.88 (dd, *J* = 8.0/0.7 Hz, 1H, ar-10-H), 9.74 (t, *J* = 5.8 Hz, 1H, ar-NH, D_2O exchange). MS (70 eV): *m/z* (%) = 387 (68) [$M^{+\bullet}$], 319 (36), 306 (48), 304 (43), 293 (53), 292 (22), 291 (17), 281 (12), 280 (58), 264 (15), 155 (13), 127 (19), 126 (31), 110 (10), 108 (29), 95 (20), 82 (75), 81 (23), 69 (18), 68 (23), 55 (27), 54 (12), 41 (19), 30 (100), 28 (63), 27 (29), 26 (13).

Biology

The Born test was performed as usual [9−11]. The thrombosis model has been described in detail [12].

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