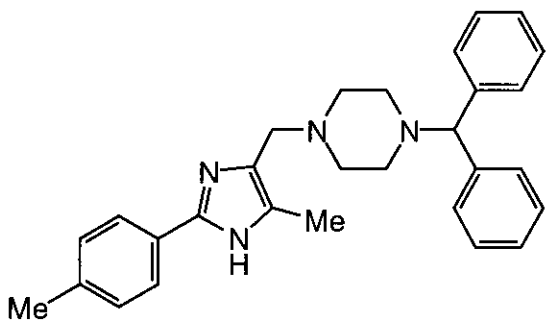
SYNTHESIS AND REARRANGEMENT OF 6*H*-IMIDAZO[1,2-*c*]-QUINAZOLIN-5-ONES

Wolf Arnold, Bernd Büttelmann*, Marie-Paule Heitz, and René Wyler

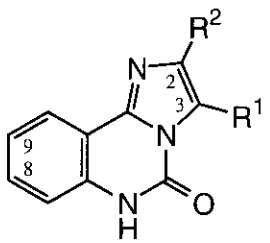
Pharma Division, Preclinical Research, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland

Abstract - The synthesis of new substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-ones (**2**) is described. 3-Substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-ones (**3**) undergo a Dimroth-type rearrangement to the thermodynamically more stable 2-substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-ones (**4**).

With its unique profile of a combined Na- and Ca-channel blocker Lifarizine (**1**) shows promising results in clinical trials as an acute therapy in stroke.[1] In an attempt to further improve bioavailability as well as binding selectivity we initiated a synthetic program aiming at rigidified analogues of type (**2**) .



1



2

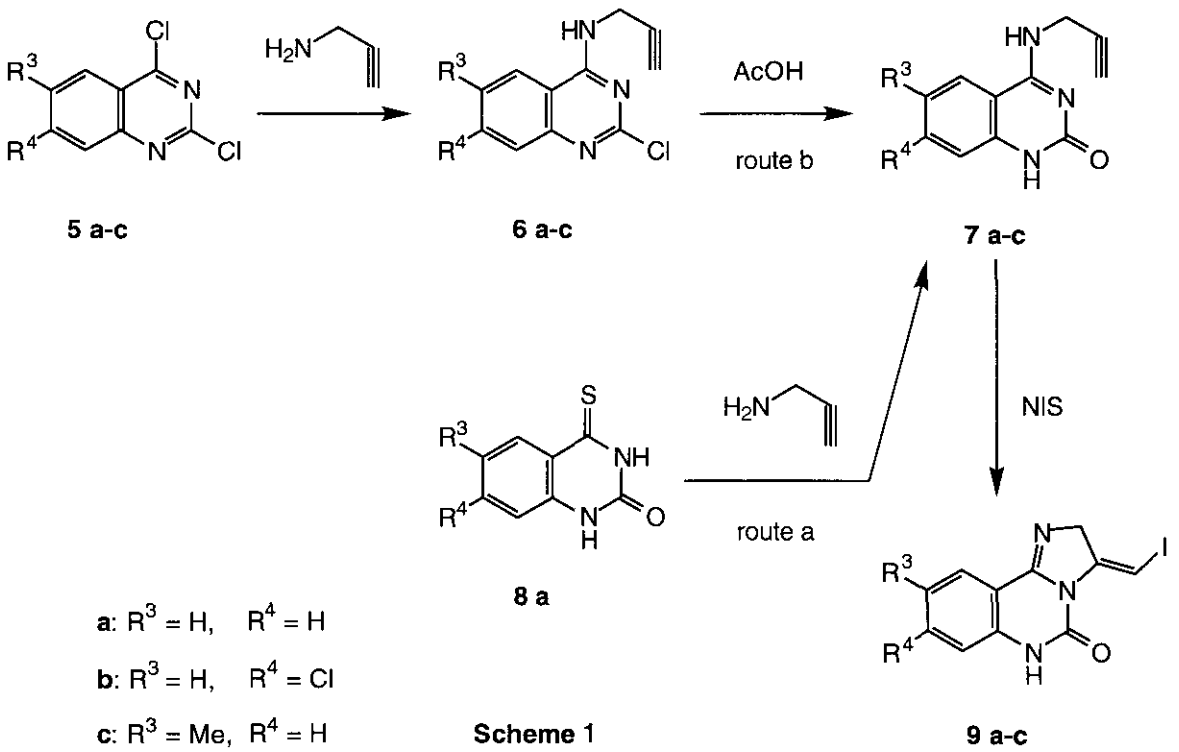
3 $R^1 = CH_2NR_2$, $R^2 = H$

4 $R^1 = H$, $R^2 = CH_2NR_2$

Synthesis of 6*H*-imidazo[1,2-*c*]quinazolin-5-ones

Compounds incorporating the 6*H*-imidazo[1,2-*c*]quinazolin-5-one moiety have previously been described: In a French patent[2] 4-amino-2-quinazolinones were cyclo-condensed with α-bromo ketones yielding 2-alkyl- or aryl-substituted compounds. In a different approach Klein and Zinner[3] reacted 2-isocyanatobenzonitriles with glycine ester or aminoacetonitrile to obtain heteroatom-substituted structures of type (**2**). The most versatile method leading to partially saturated compounds has been developed by Chern *et al.*[4] bromocyclisation of allylamino-substituted quinazolines led to 2,3-dihydro analogues of **2** carrying a bromo-methyl function as R^1 or R^2, the halogen being easily substituted with nitrogen-based

nucleophiles. By analogy, protocyclisation of propargylamino-substituted quinazolines should lead to fully aromatic 3-methyl-substituted 6*H*-imidazo[1,2-*c*]quinazolines. Following this strategy Reisch and Usifoh[5] substituted the 4-Cl in **5a** (cf. Scheme 1) with propargylamine to **6a**, which however could not be cyclised under acidic conditions.



5 a-c **6 a-c** **7 a-c**

8 a

a: R^3 = H, R^4 = H

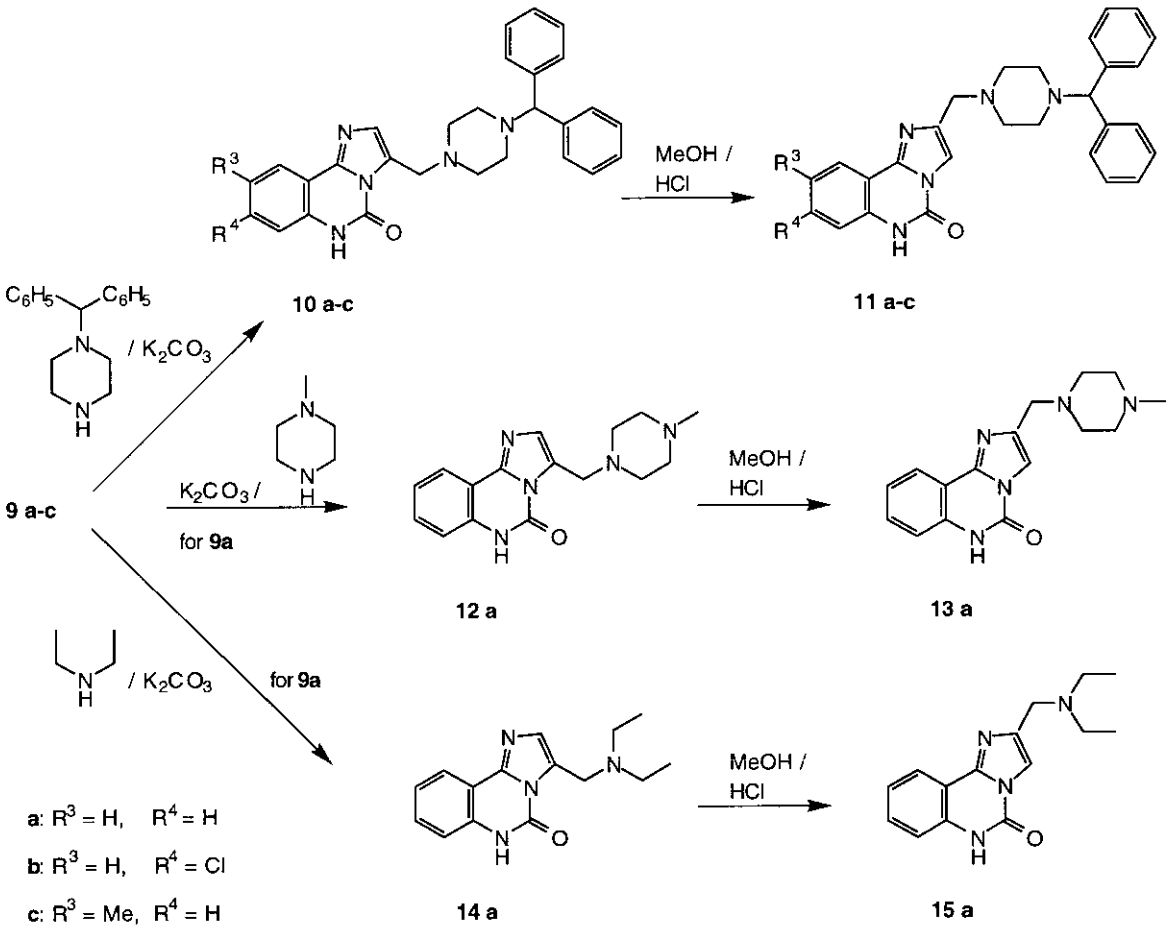
b: R^3 = H, R^4 = Cl

c: R^3 = Me, R^4 = H

Scheme 1

9 a-c

We also did not succeed to halocyclise **6a**. However, quinazolinones (**7a-c**), which are easily accessible *via* substitution of quinazolinethione (**8a**) with propargylamine (route a) or by hydrolysis of chlorides (**6a-c**) (route b) react smoothly with N-iodosuccinimide in acetic acid under sonification in a heterogeneous reaction. The resulting light-sensitive vinyl iodides (**9a-c**) can be isolated in almost quantitative yield. For **9a** the E-geometry has been established by NOE-experiments (*vide infra*). This may be explained in terms of an allowed[6] 5-exo-dig-attack of the nucleophilic urea-nitrogen at the iodirenium intermediate.[7] Vinyl iodides (**9a-c**) react with diphenylmethylpiperazine (cf. Scheme 2) under basic conditions to the desired 3-substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-ones (**10a-c**). This reaction presumably proceeds *via* an initial isomerisation of **9a-c** to the iodomethyl-substituted intermediates of type (**2**) (R^1 = CH_2I, R^2 = H), which under the reaction conditions are immediately substituted to the products of type (**3**). The latter products are stable in aprotic solvents but rearrange in protic media to 2-substituted 6*H*-imidazo[1,2-c]quinazolin-5-ones of type (**4**). The rate of the rearrangement depends on the substituents R^3 and R^4: for complete rearrangement methyl-substituted **10c** needs 3 days refluxing in acidic methanol, unsubstituted **10a** 8 hours and chloro-substituted **10b** 3 hours. Since the reaction rate is faster with electron withdrawing substituents, we assume the rearrangement to proceed *via* solvolytic attack at the carbonyl with the imidazole functioning as a leaving group (Scheme 3).

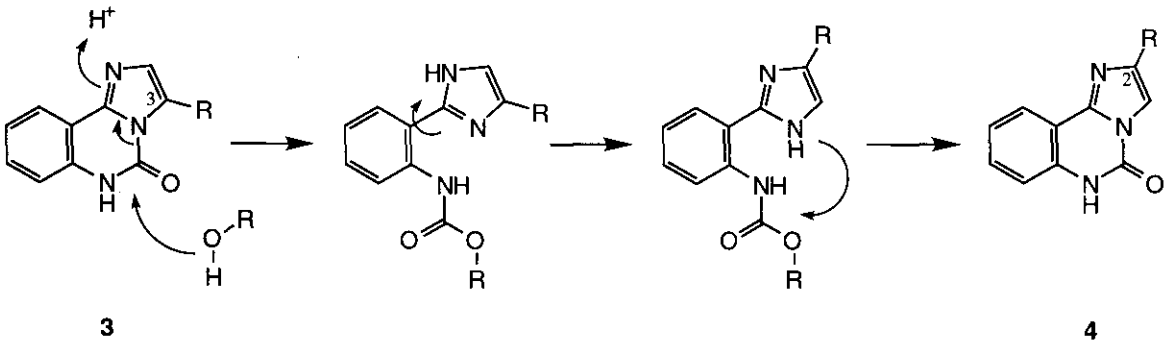


Scheme 2

Rotation about the phenyl-imidazole single bond and ring closure by the "second" imidazole nitrogen finally leads to the isomeric 2-substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-ones (**11a-c**). The rearrangement is irreversible, thus compounds of type (**4**) are thermodynamically more stable than those of type (**3**). This may be explained in terms of 1,3-allylic strain:[8] Whereas the carbonyl-group in **3** is in an eclipsing position to the large substituted methyl function, it interacts only with the small hydrogen in the case of **4**, rendering the latter thermodynamically more stable. The rearrangement is not restricted to diphenylmethylpiperazine-substituted **10a-c**, but is also observed with the more simple analogues **12a** and **14a**.

Structural assignment of 14a and 15a

The assignment of the structure of the two regioisomers of type (**3**) and type (**4**) and thus the proof of the above-mentioned rearrangement is possible by nmr. This has been performed with the diethylaminomethyl-substituted compounds (**14a**) and (**15a**): all signals of ^{1}H-nmr (400 MHz) and ^{13}C-nmr (100.6 MHz) spectra could be completely assigned using



3 4

Scheme 3

2D-$^{1}H/^{13}C$-COSY tuned to detect ^{1}J couplings (≈ 145 Hz) or long range couplings (usually ^{3}J coupling, ≈ 7 Hz). The most important difference between the spectra of the two isomers is the presence of a crosspeak between the carbonyl carbon and the imidazole proton (^{3}J coupling) in **15a**, which lacks in the spectrum of **14a**. From these results it is evident that **14a** is the 3-substituted 6*H*-imidazo[1,2-*c*]quinazolin-5-one and **15a** the 2-substituted one.

EXPERIMENTAL

Melting points are not corrected. Unless otherwise stated, ^{1}H-nmr spectra were recorded in DMSO-d_6 at 250 MHz (Bruker AC250). Chemical shifts are given in ppm relative to internal TMS. ^{1}H-decoupled ^{13}C-nmr spectra were additionally recorded with DEPT technique. Mass spectra (EI) were recorded at 70 eV ionizing voltage. Ms are presented as m/z (% rel. int.). Ir spectra were taken in KBr on a Nicolet FT ir apparatus. All chromatographic purifications are conducted with silica gel (E. Merck, 230 - 400 mesh ASTM). Starting materials were either commercial products or synthesized according to the cited literature.

2,7-Dichloro-4-(2-propynylamino)quinazoline (6b)

A solution of 8.9 g (38 mmol) of 2,4,7-trichloro-6-methylquinazoline[9] in 100 ml of THF is treated at 20 °C with 4.9 ml (76 mmol) of propargylamine and 10.7 ml (76 mmol) of triethylamine. The mixture is stirred for 12 h, then refluxed for 2 h. After removal of the solvent the residue is extractively worked up (CH_2Cl_2/H_2O) and purified by chromatography (eluent: CH_2Cl_2/MeOH = 199/1) to yield 8.3 g (87 %) of **6b**.
mp 213 °C (CH_2Cl_2/Hex); ^{1}H-nmr: 3.24 (t, J = 2.4 Hz, C≡C-H), 4.32 (d, J = 2.4 Hz, NH-CH_2), 7.63 (dd, J = 2.1 Hz, J = 8.8 Hz, 1H, arom-H), 7.73 (d, J = 2.1 Hz, 1H, arom-H), 8.30 (d, J = 8.8 Hz, 1H, arom-H), 9.32 (br s, NH-CH_2); ms (EI): 251 (73 %, M^+), 216 (100 % M^+ - Cl), 163 (53 %), 54 (65 %); ir (KBr): 3280, 2123, 1571, 1481, 1425, 1343, 1290, 939, 879, 824 cm^{-1}. Anal. Calcd for $C_{11}H_7N_3Cl_2$: C, 52.41; H, 2.80; N, 16.67; Cl, 28.13. Found: C, 52.58; H, 2.80; N, 16.75; Cl, 28.00.

2-Chloro-6-methyl-4-(2-propynylamino)quinazoline (6c)

9.2 g (43 mmol) of 2,4-dichloro-6-methylquinazoline (purity *ca.* 80 %)[10] reacted as described above for **6b**. Yield after chromatography (eluent: CH_2Cl_2/MeOH = 199/1): 6.3 g (79 %) of **6c**.
mp 176 °C (AcOEt/Hex); ^{1}H-nmr: 2.46 (s, CH_3), 3.21 (t, J = 2.5 Hz, C≡C-H), 4.31 (dd, J = 2.5 Hz, J = 5.4 Hz, NH-CH_2), 7.56 (d, J = 8.5 Hz, 1H, arom-H), 7.67 (dd, J = 8.5 Hz, J ≈ 1 Hz, 1H,

arom-H), 8.09 (d, J ≈ 1 Hz, 1H, arom-H), 9.05 (t, J ≈ 5.4 Hz, NH-CH_2); ms (EI): 231 (95 %, M^+), 196 (100 %), 143 (54 %), 54 (20 %); ir (KBr): 3433, 3327, 3238, 2222, 1630, 1580, 1534, 1419, 1340, 1288, 1188, 826 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_3Cl$: C, 62.21; H, 4.35; N, 18.14; Cl, 15.30. Found: C, 62.46; H, 4.45; N, 18.36; Cl, 15.10.

4-(2-Propynylamino)-1*H*-quinazolin-2-one (7a) route a

A suspension of 19.3 g (108 mmol) of 2-oxo-4-thiono-1,2,3,4-tetrahydroquinazoline[11] in 200 ml of ethanol is treated with 20 ml (312 mmol) of propargylamine and refluxed for 4 h. After cooling to 0 °C the solid is filtered off affording 16.33 g (76 %) of **7a**. An analytical sample is purified by chromatography (eluent CH_2Cl_2/MeOH = 95/5).
mp 222 - 223 °C (MeOH/AcOEt); ^{1}H-nmr: 3.17 (t, J = 2.4 Hz, C≡C-H), 4.26 (dd, J = 2.4 Hz, J = 5.4 Hz, NH-CH_2), 7.09 - 7.17 (m, 2H, arom-H), 7.57 (≈ dd, J ≈ 8Hz, J ≈ 8Hz, 1H, arom-H), 8.00 (d, J = 7.9 Hz, 1H, arom-H), 8.67 (t, J = 5.4 Hz, NH-CH_2); ms (EI): 199 (100 %, M^+), 171 (20 %), 118 (29 %), 54 (21 %); ir (KBr): 3419, 3201, 2103, 1653, 1597, 1547, 1456, 1349, 751 cm^{-1}. Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.26; H, 4.43; N, 20.73.

4-(2-Propynylamino)-1*H*-quinazolin-2-one (7a) route b

A solution of 3.0 g (13.8 mmol) of 2-chloro-4-(2-propynylamino)quinazoline[5] in 80 ml of acetic acid is kept for 12 h at 70 °C. After cooling to 20 °C the crystalline solid is filtered off. Yield: 3.0 g (91 %) of **7a** as hydrochloride.

3-*E*-Iodomethylene-2,6-dihydro-3*H*-imidazo[1,2-*c*]quinazolin-5-one (9a)

To a suspension of 1.5 g (7.5 mmol) of well grinded **7a** in 50 ml of acetic acid 1.9 g (8.4 mmol) of N-iodosuccinimide is added. This mixture is treated in the dark at 20 °C for 45 min in a sonification bath. After 45 min the yellow ochre solid is filtered off to yield 1.9 g (78 %) of **9a** (purity *ca.* 90 % as determined by nmr).
^{1}H-nmr (400 MHz, DMSO): 4.60 (d, J = 3.4 Hz, CH_2-N), 7.05 (t, J = 3.4 Hz, C=CIH), 7.19 (d, J = 7.6 Hz, arom-H), 7.25 (≈ t, J = 7.6 Hz, 1H, arom-H), 7.67 (≈ t, J = 7.6 Hz, 1H, arom-H), 8.03 (d, J = 7.6 Hz, 1H, arom-H), 11.50 (s, NHCO); NOE experiment: irradiation at 4.60 (methylene protons) leads to no intensity gain at 7.05 (vinyl proton) and *vice versa*; ms (EI): 325 (34 %, M^+), 198 (100 %, M^+ - I), 145 (18 %), 54 (18 %); ir (KBr): 3433, 3114, 1705, 1657, 1623, 1489, 1393, 1241, 1157, 755 cm^{-1}.

3-(4-Diphenylmethylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (10a)

A mixture of 1.0 g (3.1 mmol) of **9a**, 2.14 g (8.5 mmol) of diphenylmethylpiperazine and 1.17 g (8.5 mmol) of potassium carbonate in 10 ml of DMF is stirred for 16 h at 20 °C. At 40 °C *in vacuo* all volatile components are distilled off. The residue is partitioned between CH_2Cl_2 and water, the organic phase dried (Na_2SO_4), evaporated and subjected to chromatographic purification (eluent: CH_2Cl_2/MeOH = 98/2) to yield 820 mg (59 %) of **10a**.
mp 240 - 241 °C (EtCOMe); ^{1}H-nmr: 2.32 and 2.50 (each: ≈ br s, 4H, piperazine-CH_2), 4.06 (s, 2H, imidazole-CH_2-), 4.25 (s, N-CH (C_6H_5)$_2$), 7.10 - 7.45 (m, 13H, arom-H, imidazole-H) 7.47 (≈ t with fine splitting, J = 7.0 Hz, 1H, arom-H), 8.08 (≈ d with fine splitting, J = 7.0 Hz, 1H, arom-H), 11.78 (s, NHCO); ms (ISP): 450 (100 %, M + H^+); ir (KBr): 2819, 1724, 1575, 1451, 1330, 1269, 1006, 746, 701 cm^{-1}. Anal. Calcd for $C_{28}H_{27}N_5O$: C, 74.81; H, 6.05; N, 15.58.

Found: C, 74.60; H, 6.08; N, 15.58.

8-Chloro-3-(4-diphenylmethylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (10b)

A solution of 3.0 g (12 mmol) of **6b** in 80 ml of acetic acid is stirred for 4 h at 70 °C. The resulting suspension of **7b** is cooled to 20 °C, 2.96 g (13.2 mmol) of N-iodosuccinimide are added and the resulting mixture is kept for 45 min in a sonification bath. After filtration the yellow crystalline solid is dried at 20 °C *in vacuo* to yield 4.30 g (91 %) of **9b** as hydrochloride. This is reacted with diphenylmethylpiperazine as described for **10a**. After two successive chromatographic purifications (eluent: CH_2Cl_2/MeOH = 98/2; then CH_2Cl_2/MeOH/NH_4OH = 140/10/1) 0.97g of **10b** (19 %; note: low yield, because this compound rearranges readily to **11b**) are obtained.

mp 240 - 250 °C decomp. (Me-CO-Et); ^{1}H-nmr: 2.34 and 2.50 (each: ≈ br s, 4H, piperazine-CH_2), 4.04 (s, imidazole-CH_2-), 4.26 (s, N-CH (C_6H_5)$_2$), 7.10 - 7.48 (m, 13H, arom-H, imidazole-H), 8.06 (d, J = 9.0 Hz, 1H, arom-H), 11.88 (s, NHCO); ms (ISP): 484 (100 %, M +H^+); ir (KBr): 3026, 2810, 1731, 1620, 1592, 1449, 1298, 1135, 1005, 753, 706 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_5OCl$: C, 69.48; H, 5.41; N, 14.47; Cl, 7.32. Found: C, 69.05; H, 5.47; N, 14.38; Cl, 7.20.

3-(4-Diphenylmethylpiperazin-1-ylmethyl)-9-methyl-6*H*-imidazo[1,2-*c*]quinazolin-5-one (10c)

A solution of 1.5 g (6.5 mmol) of **6c** in 40 ml of acetic acid is stirred for 16 h at 70 °C. The resulting suspension is treated as described for **10b**. After chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 250/10/1) 1.72 g (57 % from **6c**) of **10c** are obtained.

mp > 250 °C (CH_2Cl_2/Hex); ^{1}H-nmr: 2.32 and 2.50 (each: ≈ br s, 4H, piperazine-CH_2), 2.38 (s, CH_3), 4.05 (s, imidazole-CH_2-), 4.25 (s, N-CH (C_6H_5)$_2$), 7.10 - 7.45 (m, 13H, arom-H, imidazole-H), 7.89 (≈ s, 1H, arom-H), 11.68 (s, NHCO); ms (ISP): 464 (100 %, M + H^+); ir (KBr): 2808, 1720, 1602, 1451, 1331, 1135, 1006, 852, 755, 705 cm^{-1}. Anal. Calcd for $C_{29}H_{29}N_5O$: C, 75.14; H, 6.31; N, 15.11. Found: C, 74.98; H, 6.31; N, 15.16.

2-(4-Diphenylmethylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (11a)

A solution of 0.93 g (2.1 mmol) of **10a** in 100 ml of methanol and 20 ml of 1N aqueous HCl is refluxed for 8 h. After addition of 20 g silica and 20 ml of 1N aqueous NaOH all volatile components are removed at 60 °C *in vacuo* and the residue subjected to chromatographic purification (eluent: CH_2Cl_2/MeOH = 195/5) to yield 0.60 g (65 %) of **11a**.

mp 202 - 203 °C (EtCOMe); ^{1}H-nmr: 2.33 and 2.50 (each: ≈ br s, 4H, piperazine-CH_2), 3.58 (s, imidazole-CH_2-), 4.26 (s, N-CH (C_6H_5)$_2$), 7.10 - 7.48 (m, 12H, arom-H), 7.51 (t with fine splitting, J = 7.1 Hz, 1H, arom-H), 7.67 (s, imidazole-H), 8.10 (d with fine splitting, J = 7.1 Hz, 1H, arom-H), 11.96 (br s, NHCO); ms (ISP): 450 (100 %, M + H^+); ir (KBr): 2816, 1723, 1596, 1450, 1305, 1134, 1007, 751, 702 cm^{-1}. Anal. Calcd for $C_{28}H_{27}N_5O$: C, 74.81; H, 6.05; N, 15.58. Found: C, 74.64; H, 6.30; N, 15.54.

8-Chloro-2-(4-diphenylmethylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (11b)

Rearrangement of 0.30 g (0.62 mmol) of **10b** is performed as described for **11a** and takes 3 h

for completion. Chromatographic purification (eluent: CH_2Cl_2/MeOH = 95/5) yields 0.21 g (70 %) of **11b**.
mp 285 - 286 °C (EtCOMe); ^{1}H-nmr: 2.33 and 2.50 (each: ≈ br s, 4H, piperazine-C$\underline{H}_2$), 3.57 (s, imidazole-C$\underline{H}_2$-), 4.26 (s, N-C$\underline{H}$ (C_6H_5)$_2$), 7.10 - 7.45 (m, 12H, arom-$\underline{H}$), 7.68 (s, imidazole-$\underline{H}$), 8.09 (d, J = 8.9 Hz, 1H, arom-$\underline{H}$), 12.07 (br s, N$\underline{H}$CO); ms (ISP): 484 (100 %, M + H^+); ir (KBr): 2815, 1715, 1589, 1450, 1396, 1303, 1132, 1009, 859, 747, 706 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_5OCl$: C, 69.48; H, 5.41; N, 14.47; Cl, 7.32. Found: C, 69.02; H, 5.54; N, 14.12; Cl, 7.65.

2-(4-Diphenylmethylpiperazin-1-ylmethyl)-9-methyl-6*H*-imidazo[1,2-*c*]quinazolin-5-one (11c)
Rearrangement of 1.72 g (3.7 mmol) of **10c** is performed as described for **11a** and takes 72 h for completion. Chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 190/10/1) yields 1.50 g (87 %) of **11c**.
mp 249 °C (EtCOMe); ^{1}H-nmr: 2.32 and 2.50 (each: ≈ br s, 4H, piperazine-C$\underline{H}_2$), 2.39 (s, C$\underline{H}_3$), 3.57 (s, imidazole-C$\underline{H}_2$-), 4.26 (s, N-C$\underline{H}$ (C_6H_5)$_2$), 7.10 - 7.45 (m, 12H, arom-$\underline{H}$), 7.65 (s, imidazole-$\underline{H}$), 7.91 (s, 1H, arom-$\underline{H}$), 11.88 (br s, N$\underline{H}$CO); ms (ISP): 464 (100 %, M + H^+); ir (KBr): 2808, 1715, 1599, 1543, 1505, 1451, 1394, 1010, 746, 705 cm^{-1}. Anal. Calcd for $C_{29}H_{29}N_5O$: *C 75.14, H 6.31, N 15.11. Found: C 74.81, H 6.39, N 14.95.*

3-(4-Methylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (12a)
As described for **10a**, 3.9 g (12 mmol) of **9a** are brought to reaction with 3.3 g (33 mmol) of 1-methylpiperazine. After chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 110/10/1) 1.35 g (38 %) of **12a** are obtained.
mp 206 °C (CH_2Cl_2/Hex); ^{1}H-nmr: 2.15 (s, N-C$\underline{H}_3$), 2.33 and 2.50 (each: ≈ br s, 4H, piperazine-C$\underline{H}_2$), 4.02 (s, imidazole-C$\underline{H}_2$-), 7.23 (s, imidazole-$\underline{H}$), 7.25 - 7.36 (m, 2H, arom-$\underline{H}$), 7.49 (t with fine splitting, J = 7 Hz, 1H, arom-$\underline{H}$), 8.08 (d with fine splitting, J = 7 Hz, 1H, arom-$\underline{H}$), 11.78 (s, N$\underline{H}$CO); ms (ISP): 298 (100 %, M + H^+); ir (KBr): 2930, 2792, 1732, 1600, 1477, 1330, 1160, 752 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_5O$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.31; H, 6.44; N, 23.37.

2-(4-Methylpiperazin-1-ylmethyl)-6*H*-imidazo[1,2-*c*]quinazolin-5-one (13a)
Rearrangement of 0.70 g (2.4 mmol) of **12a** is performed as described for **11a** and takes 8 h for completion. Chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 140/10/1) yields 0.40 g (57 %) of **13a**.
mp 249 - 250 °C (CH_2Cl_2/Hex); ^{1}H-nmr: 2.14 (s, N-C$\underline{H}_3$), 2.33 and 2.50 (each: ≈ br s, 4H, piperazine-C$\underline{H}_2$), 3.54 (s, imidazole-C$\underline{H}_2$-), 7.25 - 7.40 (m, 2H, arom-$\underline{H}$), 7.54 (t with fine splitting, J = 7 Hz, 1H, arom-$\underline{H}$), 7.67 (s, imidazole-$\underline{H}$), 8.12 (d with fine splitting, J = 7 Hz, 1H, arom-$\underline{H}$), 11.97 (br s, N$\underline{H}$CO); ms (ISP): 298 (100 %, M + H^+); ir (KBr): 2935, 2804, 1726, 1595, 1476, 1320, 1141, 748 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_5O$: C, 64.63; H, 6.44; N; 23.55. Found: C, 64.46; H, 6.51; N, 23.34.

3-Diethylaminomethyl-6*H*-imidazo[1,2-*c*]quinazolin-5-one (14a)
A suspension of 0.65 g (2.0 mmol) of **9a** in 10 ml of diethylamine is stirred at 20 °C for 36 h. Workup as described for **10a** yields after chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 90/10/1) 0.35 g (65 %) of **14a**.

mp 181 - 182 °C (AcOEt/iPr ether); ^{1}H-nmr (400 MHz, DMSO): 1.03 (t, J = 7.1 Hz, [CH_2-CH_3]2), 2.53 (q, J = 7.1 Hz, [CH_2-CH_3]2), 3.68 (s, imidazole-CH_2-), 7.31 (dd, J ≈ 7.4 Hz, J ≈ 8 Hz, 1H, C9-H) 7.37 (≈ d, J ≈ 8.2 Hz, 1H, C7-H), 7.54 (≈ dd, J ≈ 8 Hz, J ≈ 7.5 Hz, 1H, C8-H), 7.65 (s, C2-H), 8.10 (≈ d, J ≈ 7.4 Hz, 1H, C10-H), 11.9 (br s, NHCO); ^{13}C-nmr (101 MHz, DMSO): 12.14 (CH_2-CH_3)2, 46.49 (CH_2-CH_3)2, 50.09 (CH_2- imidazole), 111.34 (C-2), 112.33 (C-10a), 116.01 (C-7), 122.88 (C-10), 123.49 (C-9), 130.43 (C-8), 135.24 (C-6a), 142.90 and 143.06 (C-1a and C-3), 145.04 (C=O); ms (EI): 270 (2 %, M^+), 241 (81 %), 198 (100 %), 145 (11 %), 72 (13 %), 54 (14 %); ir (KBr): 2969, 2929, 1727, 1600, 1477, 1390, 1329, 1261, 749 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.31; H, 6.76; N, 20.57.

2-Diethylaminomethyl-6*H*-imidazo[1,2-*c*]quinazolin-5-one (15a)

Rearrangement of 2.06 g (2.1 mmol) of **14a** is performed as described for **11a** and takes 8 h for completion. Chromatographic purification (eluent: CH_2Cl_2/MeOH/NH_4OH = 90/10/1) yields 1.34 g (65 %) of **15a**.

mp 159 - 160 °C (AcOEt/iPr ether); ^{1}H-nmr (400 MHz, DMSO): 1.00 (t, J = 7.1 Hz, [CH_2-CH_3]2), 2.53 (q, J = 7.1 Hz, [CH_2-CH_3]2), 4.10 (s, imidazole-CH_2-), 7.22 (s, C3-H), 7.25 - 7.36 (m, 2H, C9-H and C7-H), 7.49 (≈ t with fine splitting, J = 7.1 Hz, 1H, C8-H), 8.08 (≈ d, J = 7,1 Hz, 1H, C10-H), 11.7 (br s, NHCO); ^{13}C-nmr (101 MHz, DMSO): 12.03 (CH_2-CH_3)2, 46.57 (CH_2-CH_3)2, 48.42 (CH_2- imidazole), 112.79 (C-10a), 115.58 (C-7), 122.64 (C-10), 123.37 (C-9), 129.63 (C-2), 130.19 (C-8), 130.80 (C-3), 135.20 (C-6a), 143.96 (C-1a), 146.54 (C=O); ms (EI): 270 (2 %, M^+), 241 (2 %), 199 (100 %), 171 (8 %), 145 (8 %), 72 (46 %); ir (KBr): 3150, 2929, 1733, 1701, 1595, 1478, 1368, 746 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.43; H, 6.82; N, 20.70.

REFERENCES

1. C.P. Taylor and B.S. Meldrum, *TIPS*, 1995, **16**, 309.
2. J.J. Bourguignon, C.G. Wermuth, J.F. Renaud de la Faverie, C. Thollon, and A.Lombet, *Eur. Pat.* 446141, March 08, 1991 (*Chem. Abstr.*, 1992, **116**, 21068).
3. H. Klein and G. Zinner, *Chem Ztg.*, 1987, **111**, 373.
4. J.W. Chern, P.L. Tao, M.H. Yen, G.Y. Lu, C.Y. Shiau, Y.J. Lai, S.L. Chien, and C.H. Chan, *J. Med. Chem.*, 1993, **36**, 2196.
5. J. Reisch and C. Usifoh, *J. Heterocycl. Chem.*, 1993, **30**, 659.
6. J. Baldwin, *J. Chem. Soc., Chem. Comm.*, 1976, 734.
7. for a related case cf.: G. Capozzi, C. Caristi, and M Gattuso, *J. Chem. Soc., Perkin Trans. 1*, 1984, 255.
8. for a review cf.: R.W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
9. H.S. Curd, E. Hoggarth, J.K. Landquist, and F.L. Rose, *J. Chem. Soc.*, 1948, 1759.
10. V. Oakes, H.N. Rydon, and K. Undheim, *J. Chem. Soc.*, 1962, 4678.
11. D.L. Trepanier, S. Sunder, and W.H. Braun, *J. Heterocycl. Chem.*, 1974, **11**, 747.

Received, 5th July, 1996