ACCESS TO QUINAZOLINES FROM 2-NITROBENZALDEHYDE AND ARYLAMINES

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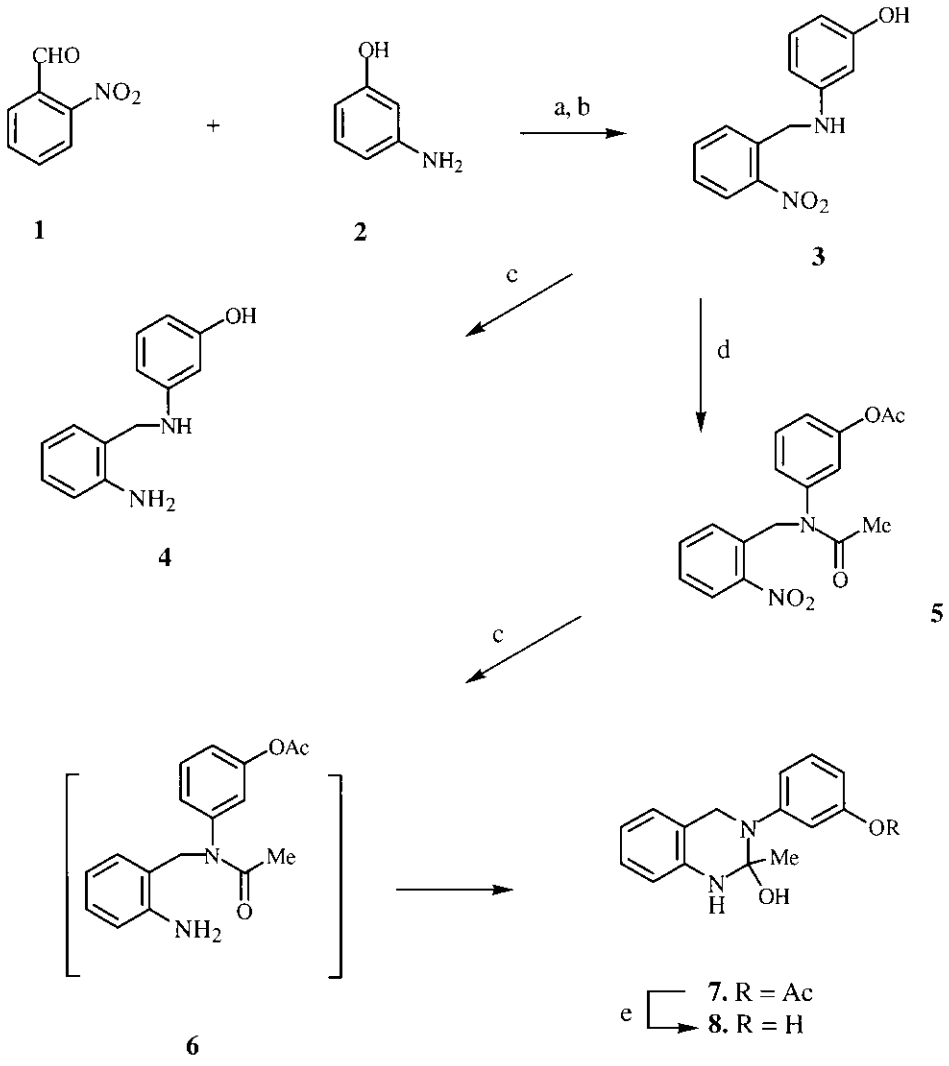
Abstract- A synthesis of *N*-(2-nitrobenzyl)acetanilide (**5**) and (**11**) from 2-nitrobenzaldehyde and aromatic amines is reported. The reaction of amides (**5**) and (**11**) with iron in acetic acid-ethanol-water provided the corresponding 3-phenyl-π1,2,3,4-tetrahydroquinazolines (**7**) and (**12**). Reductive cyclization of 1-acetyl-2-(2-nitrophenyl)-benzimidazol (**16**) to benzimidazø[1,2-*c*]quinazoline (**19**) and benzimidazol (**20**) is described.

A well established method to construct symmetrical Tröger's base analogues[1] is based on the condensation of arylamines with formaldehyde in acid media. The reaction mechanism was proposed by Wagner[2] and Farrer[3] and some steps of the complex reactions sequence have been elucidated by Spielman[4] and Wilcox.[5] On the basis of the Spielman's result the formation of the benzodiazocine framework of the Tröger's base occurs in the last step, *via* an acid-induced tandem reaction of a 3-phenyl-1,2,3,4-tetrahydroquinazoline and formaldehyde. Wilcox *et al.*[5] had reported the preparation of the Tröger's base and unsymmetrical analogues by reaction of *N*-(2-aminobenzyl)aniline and formaldehyde. This method allows the synthesis of Tröger's bases containing a variety of substituents on the aromatic rings.[5,6]

In connection with our project on the synthesis of cytotoxic heterocyclic quinones[7-13] we decided to explore the scope of the Wilcox methodology[5] to the synthesis of dibenzodiazocines containing a latent quinone nucleus. The synthesis of the diamine (**4**), a suitable precursor for our purpose (Scheme 1), was attempted starting from aldehyde (**1**) and arylamine (**2**).

Condensation of these compounds followed by reduction of the imine intermediate with sodium borohydride provided **3** in 72% yield. Compound (**3**) was submitted to reduction with iron in acetic acid-ethanol-water solution under mild condition (50-60 °C, 45 min),[14] however the efforts to isolate amine (**4**) were unsuccessful. In order to circumvent this difficult the access to **3** was attempted through amide (**5**).

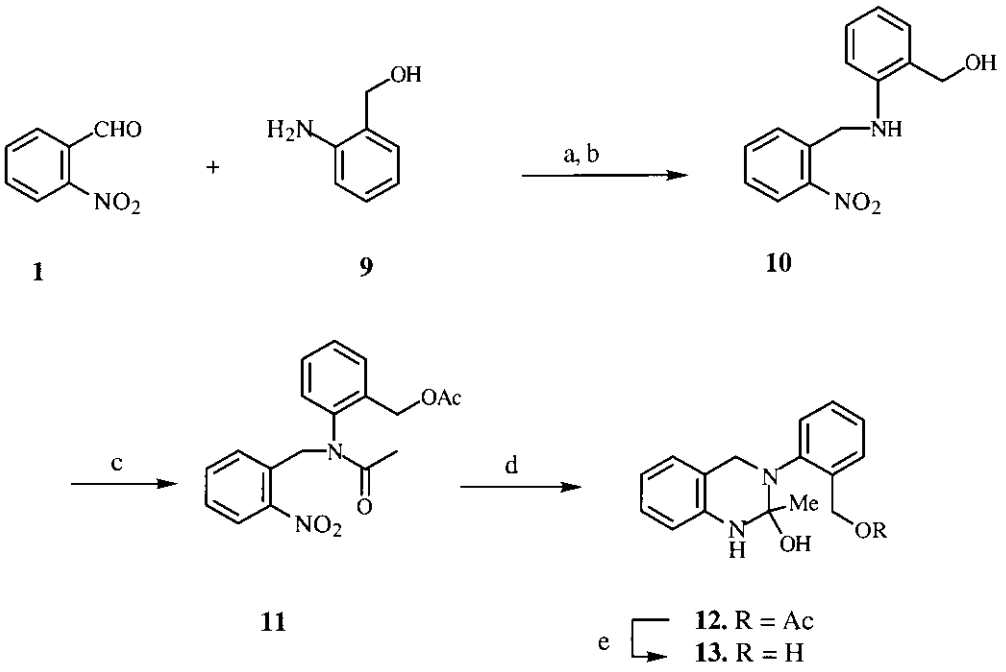


Reagents: a) EtOH, rt; b) $NaBH_4$, EtOH; c) Fe, AcOH, EtOH, H_2O; d) Ac_2O, rt; e) K_2CO_3, MeOH

Scheme 1

Amide (**5**) was prepared by acetylation of **3** with acetic anhydride and then submitted to reduction with iron under the above mentioned conditions. Interestingly, the reaction afforded a mixture of tetrahydroquinazoline (**7**) along with low amounts of the hydrolysis product (**8**). Attempts to purify quinazoline (**7**) were unsuccessful, therefore the mixture was reacted with potassium carbonate in methanol to provide quinazoline (**8**). It is noteworthy that quinazoline (**8**) was inert to dehydration in acid media.

In the light of these results we planned the synthesis of quinazoline (**13**) through the same synthetic sequence employed for the preparation of **8** (Scheme 2). Our interest in quinazoline (**13**) is due to its potential use as precursor of Tröger's base analogues. The hydroxymethyl group in the phenyl substituent of **13** would be useful to construct the endomethylene bridge of the dibenzodiazocine framework.



Reagents: a) EtOH, rt; b) $NaBH_4$, EtOH; c) Ac_2O, rt; d) Fe, AcOH, EtOH, H_2O; e) K_2CO_3, MeOH

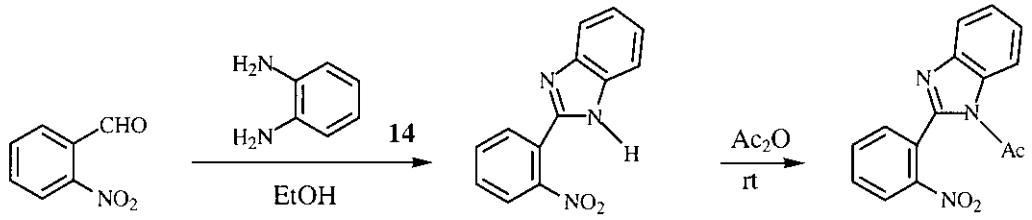
Scheme 2

Amine (**10**) was prepared in 97% yield by the usual method from 2-nitrobenzaldehyde (1) and 2-aminobenzyl alcohol (**9**) followed by acetylation of **10** to provide compound (**11**). It is noteworthy that the ^{1}H NMR spectrum of **11** displays an AB and an AX system (see experimental) for the protons of the two methylene groups indicating an hindered rotation of the molecule. Since no restricted molecular rotation was detected in amide (**5**) the hindered rotation of compound (**11**) could be attributed to the presence of the acetyloxymethyl group at the *orto* position.

Compound (**11**) was subjected to reduction with iron under the usual condition to give the expected quinazoline (**12**) in 80 % yield. Compound (**12**) was allowed to react with potassium carbonate in methanol to afford quinazoline (**13**) in 80% yield.

The ^1H NMR spectrum of **12** and **13** revealed inhibition to the molecular rotation probably due to the presence of the CH_2OAc and CH_2OH substituents at *orto* position in the phenyl group.

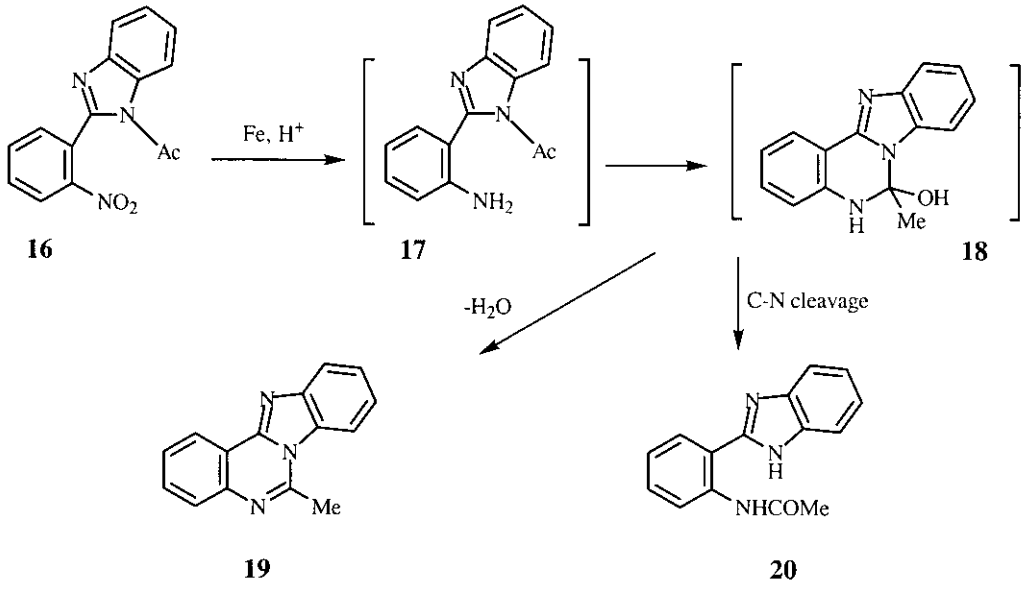
In order to extend the scope of the above access to fused quinazolines we next examined the reactivity of benzimidazol (**16**) to the reductive cyclization. This compound was obtained from nitroimidazol (**15**) which was prepared from 2-nitrobenzaldehyde (**1**) and 1,2-phenylenediamine (**14**) (Scheme 3).



1 **15** **16**

Scheme 3

When compound (**16**) was subjected to the usual reductive treatment benzimidazoquinazoline (**19**) and benzimidazol (**20**) were isolated instead of the expected fused quinazoline (**18**) which was not detected in the reaction mixture. The formation of heterocycles (**19**) and (**20**) from **16** probably is mediated by quinazoline (**18**) as outlined in Scheme 4.



16 **17** **18**

19 **20**

Scheme 4

Transacylation reaction of **17** to **20** is a favorable competitive process to dehydration reaction because the stabilization of the imidazol ring through the lone pair on the nitrogen atom in **17** is much less effective than in benzimidazol (***20***).

Taking into accounts the formation of 2-hydroxy-1,2,3,4-tetrahydroquinazolines (**7**) and (**12**) by reductive cyclization of **5** and **11**, dehydration of quinazoline intermediate (**18**) to give **19** under similar conditions was an unexpected reaction. Nevertheless, it is reasonable to assume that in this case the elimination reaction is a favored process due to the coplanarity of the tetracyclic skeleton of product (**19**).

In summary, a practical access to functionalized 3-phenyl-1,2,3,4-tetrahydrohydroquinazolines (**8**) and (**13**) and the benzimidizoquinazoline (**19**) by reductive cyclization of easily available *N*-(2-nitrobenzyl)acetanilide amides (**5**), (**11**) and 2-(2-*o*-nitrophenyl)benzimidazol (**16**) was developed.

EXPERIMENTAL

General. All reagents were of commercial quality, reagent grade, and were used without further purification. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were recorded on a FT Bruker spectrophotometer for KBr. The ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DRX-300 spectrometer. The solvent used for NMR spectra was deuteriochloroform unless otherwise stated. Chemical shifts are given in the δ (ppm) scale downfield from TMS, and coupling constants (*J*) are given in Hertz. EIMS were recorded on a Fisons MD 800. Silica gel Merck 60 (70-230 mesh), and DC-Alufolien 60F_{254} were used for preparative column and analytical TLC.

3-(2-Nitrobenzylamino)phenol (3) A solution of 2-nitrobenzaldehyde (**1**) (362 mg; 2.4 mmol) and 3-aminophenol (**2**) (260 mg, 2.60 mmol) in ethanol (50 mL) was refluxed for 7 h and the mixture was left overnight at rt. The solution was treated at rt with $NaBH_4$ (180 mg, 4.70 mmol) in small portions for 2h and the reaction mixture was stirred overnight. The mixture was diluted with water (20 ml), extracted with chloroform (3 x 30 ml) then worked up as usual. The crude product was purified by column chromatography (CH_2Cl_2-AcOEt = 3:1) to give pure **3** as an yellow-brown oily liquid (420 mg, 72%); IR: 3371, 1617; ^{1}H NMR (300 MHz) δ 4.69 (s, 2H, CH_2), 4.74 (s, 1H, NH), 6.04 (d, 1H, *J* = 2.3, 2-H), 6.18 (m, 2H, 4- and 6-H), 6.99 (t, 1H, *J* = 8, 5-H), 7.41 (dt, 1H, *J* = 8.5, 1.5, 4'-H), 7.56 (dt, 1H, *J* = 8,5, 1.2, 5'-H), 7.65 (dd, 1H, *J* = 8.5, 1.2, 6'-H), 8.06 (dd, 1H, *J* = 8.5, 1.2, 3'-H); ^{13}C NMR (75 MHz): δ 45.8, 100.1, 105.3, 106.1, 125.3, 128.1, 129.9, 130.47, 133.9, 135.6, 148.3, 149.1, 156.9. *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.63; H, 5.08; N, 11.47.

3-[*N*-Acetyl-*N*-(2-nitrobenzylamino)]phenyl acetate (5) A solution of 3 (42 mg, 0.128 mmol) in acetic anydride (5 mL) was allowed to stand rt overnight. The mixture was poured into ice-water (30 mL) and then stirred for 2 h. The whole was neutralized with sodium hydrogencarbonate, extracted with chloroform (2 x 25 mL) and the dried extract was evaporated under *vacuo*. The crude product was column chromatographied (chloroform-ethyl acetate = 2:1) to afford pure 5 (50 mg, 86 %); mp 151-152.5 °C; IR:

1758, 1671, 1523, 1344; ^{1}H NMR (300 MHz, DMSO-d_6): 1.93 (s, 3H, Me), 2.27 (s, 3H, Me), 5.18 (s, 2H, CH_2), 7.00-8.00 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 20.7, 22.3, 49.3, 121.2, 121.4, 124.6, 124.9, 128.4, 129.4, 100.1, 132.0, 133.6, 143.4, 148.0, 150.8, 168.9, 169.0; *Anal.* Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.22; H, 4.93; N, 8.65.

3-(3-Acetyloxyphenyl)-2-hydroxy-2-methyl-1,2,3,4-tetrahydroquinazoline (7) A suspension of compound (**5**) (210 mg, 0.64 mmol) and powder iron (800 mg, 14.2 mmol) in acetic acid-ethanol-water (50 mL, 1:1:1 v/v) was heated at 50-60°C with stirring for 45 min. The mixture was diluted with water (20 mL), neutralized with sodium hydrogencarbonate, and extracted with ethyl acetate (3 x 50 mL). The dried extract was evaporated *in vacuo* to give crude quinazoline (**7**) as a pale yellow oily liquid (180 mg). Attempts to obtain an analytical sample of quinazoline (**7**) by recrystallization (ethanol-light petroleum = 2:1), column chromatography ($CHCl_3$-AcOEt = 2:1) and preparative TLC (ethyl acetate-chloroform =1:1) were unsuccessful. ^{1}H NMR (300 MHz, $CDCl_3$+D_2O): δ 2.08 (s, 3H, 2-Me), 2.28 (s, 3H, OCOMe), 4.22 (s, 2H, CH_2-N), 6.40-6.70 (m, 5H, Ar-H), 6.80-7.20 (m, 3H, Ar-H); EIMS *m/e* (%): 298 (M^+, 41), 280 (30), 255 (64), 213 (74), 148 (76), 106 (100).

3-(3-Hydroxyphenyl)-2-hydroxy-2-methyl-1,2,3,4-tetrahydroquinazoline (8) A suspension of crude **7** (182 mg, 0.6 mmol) and potassium carbonate (100 mg, 0.94 mmol) in methanol (20 mL) was stirred at rt for 3 h. The mixture was filtered and the filtrate was diluted with water (20 mL). The solution was extracted with ethyl acetate (2 x 20 mL) and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent afforded crude quinazoline (**8**) Column cromatography (chloroform-ethyl acetate = 1:1) followed by preparative TLC provided pure **8** (53 mg, 35%); mp 144-145 °C; IR: 3446, 3399, 3368, 1612, 1586; ^{1}H NMR (300 MHz): δ 1.85 (s, 3H, Me), 4.78 (s, 2H, CH_2-N), 6.44-7.19 (m, 8H, Ar-H); ^{13}C NMR (75 MHz): δ 22.8, 50.5, 115.7, 116.1, 116.2, 118.0, 120.0, 120.59, 129.70, 130.9, 132.6, 143.1, 145.8, 158.0, 172.2; *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29, N, 10.93. Found: C, 70.75; H, 6.30; N, 10.93

2-[*N*-(2-Nitrobenzyl)amino]benzyl alcohol (10) A solution of 2-nitrobenzaldehyde (**1**) (393 mg, 2.6 mmol) and 2-aminobenzyl alcohol (**9**) (320 mg, 2.60 mmol) in ethanol (50 mL) was refluxed for 4 h. The solution was treated with $NaBH_4$ (300 mg, 7.93 mmol) at rt in small portion for 2 h and the reaction mixture was stirred overnight. The mixture was diluted with water (40 mL) and extracted with chloroform (3 x 30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a brown oily liquid. Crude was purified by column chromatography on silica gel (CH_2Cl_2-AcOEt = 3:1) followed by preparative TLC (chloroform) to afford pure **10** (450 mg, 68%) as an yellow-brown oily liquid; ^{1}H NMR (300 MHz): δ 4.70 (s, 2H, CH_2-N), 4.75 (s, 2H, CH_2-O), 6.40 (d, 1H, J = 8.0, Ar-H), 6.66 (t, 1H, J = 9, Ar-H), 7.05-7.55 (m, 5H, Ar-H), 8.21 (d, H, J = 8.0, Ar-H); ^{13}C NMR (75 MHz): δ 45.1, 64.8, 110.9, 117.2,

122.8, 124.6, 125.2, 128.4, 129.3, 129.5, 129.6, 133.7, 135.6, 148.4; *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.09; H, 5.29; N, 10.54. Found: C, 64.50; H, 5.29; N, 10.54.

2-[*N*-Acetyl-*N*-(2-nitrobenzyl)amino]benzyl acetate (11) A solution of **10** (416 mg, 11.7 mmol) in acetic anhydride (20 mL) was left at rt for 24 h. The mixture was poured into ice-water, stirred for 4h and neutralized with sodium hydrogencarbonate. The mixture was extracted with chloroform (2 x 25 mL) and the extract was dried over sodium sulfate. and evaporated *in vacuo*. Further recrystallization from water-ethanol afforded pure **11** (4260 mg, 78%), white needles, mp 125-126.5 °C; IR: 1726, 1653, 1529, 1247; ^{1}H NMR (300 MHz): δ 1.88 (s, 3H, OCOMe), 2.11 (s, 3H, NCOMe), 4.82 (d, 1H, *J* = 16, Ar-C*H*H-N), 4.94 (d, 1H, *J* = 12.5, C*H*HOCOMe), 5.07 (d, 1H, *J* = 12.5, CH*H*OCOMe), 5.68 (d, 1H, *J* = 16, Ar-CH*H*-N), 6.89 (dd, 2H, *J* = 1.1, 7.8, 6-H), 7.27-7.72 (m, 6-H, Ar-H), 7.87 (dd, 1H, *J* = 1.1, 8.2, 3'-H); ^{13}C NMR (75 MHz): δ 21.2, 22.8, 49.2, 62.7, 125.1, 128.8, 129.5, 129.6, 130.4, 131.4, 131.8, 132.6, 133.7, 134.1, 141.8, 149.4, 170.9, 171.6; *Anal.* Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.17; H, 5.33; N, 8.35.

3-(2-Acetyloxymethylphenyl)-2-hydroxy-2-methyl-1,2,3,4-tetrahydroquinazoline (12) Asuspension of **11** (300 mg, 0.87 mmol) and powder iron (800 mg, 14.3 mmol) in acetic acid-ethanol-water (30 mL, 1:1:1 v/v) was heated at 50-60°C with stirring for 45 min. The mixture was diluted with water, neutralized with sodium hydrogencarbonate, and extracted with ethyl acetate (2 x 30 mL). The extract was dried over sodium sulfate and evaporated under *vacuo* to give a pale yellow oil. Column chromatography provided **12** as an oil (220 mg, 80%) which solidified on standing, mp 92-93.5 °C; IR: 3376, 3236, 1742, 1629; ^{1}H NMR (300 MHz): δ 1.83 (s, 3H, 2-Me), 2.06 (s, 3H, OCOMe), 4.55-4.90 (m, 4H, CH_2-N and CH_2-OAc), 6.30-7.50 (m, 8H, Ar-H); ^{13}C NMR (75 MHz): δ 21.2, 22.8, 50.3, 62.3, 115.7, 117.3, 119.4, 129.16, 129.9, 130.0, 130.1, 130.6, 132.4, 134.7, 140.7, 146.5, 170.9, 171.8; *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.23; H, 6.41; N, 8.97. Found: C, 69.33; H, 6.48; N, 9.02.

2-Hydroxy-3-(2-hydroxymethylphenyl)-2-methyl-1,2,3,4-tetrahydroquinazoline (13) A suspension of quinazoline (**12**) (187 mg, 0.60 mmol) and sodium carbonate (1 g, 7.2 mmol) in methanol (20 mL) was magnetically stirred or 2 h at rt. The mixture was filtered and the filtrate was partitioned between water-ethyl acetate. The organic layer was washed with water and dried over sodium sulfate to afford crude quinazoline (**13**). The solvent was evaporated off and the residue was chromatographied on silica gel (chloroform-ethyl acetate = 1:1) to give pure quinazoline (**13**) (123 mg, 80%) as a white solid, mp 116-117 °C; IR: 3418, 3347, 3262, 1616; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O): δ 1.77 (s, 3H, 2-Me), 4.15, (d, 1H, *J* = 13, C*H*H-N), 4.19, (d, 1H, *J* = 13, CH*H*-N), 4.46 (d, 1H, *J* = 14.3, C*H*H-OH), 5. 17 (d, 1H, *J* = 14.3, CH*H*-OH), 6.39-7.48 (m, 8H, Ar-H); ^{13}C NMR (75 MHz): δ 22.8, 47.9, 64.5, 115.9, 117.4, 129.0, 129.3, 129.33, 129.6, 130.0, 130.3, 132.5, 139.6, 139.9, 146.4, 172.1; *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.08; H, 6.72; N, 10.37. Found: C, 70.95; H, 6.67; N, 10.15.

2-(2-Nitrophenyl)benzimidazol (15) A solution of 2-nitrobenzaldehyde (**1**) (150 mg, 0.99 mmol) and 1,2-phenylenediamine (**14**) (107 mg, 0.99 mmol) in ethanol (20 mL) was heated under reflux overnight. The reaction mixture was diluted with water and extracted with chloroform (3 x 30 mL). The extract was washed with water, dried over magnesium sulfate and evaporated under *vacuo*. The crude was recrystallized from ethanol to give pure benzimidazol (**15**) (191 mg, 80%), mp 277-278.5 °C; IR: 3440, 1526; ^{1}H-NMR (300 MHz): δ 7.25-8.00 (m, 8H, Ar-H), 12.38 (br s, 1H, NH); ^{13}C NMR (75 MHz): δ 111.8, 119.8, 122.2, 123.3, 124.6, 130.5, 132.2, 132.8, 139.2, 142.6, 148.0, 148.9, 178.5; *Anal.* Calcd for $C_{13}H_9N_3O_2$: C, 65.26; H, 3.79; N, 17.57. Found: C, 64.90; H, 4.09; N, 17.34

1-Acetyl-2-(2-nitrophenyl)benzimidazol (16) A solution of **15** (191 mg, 0.798 mmol) in acetic anhydride (5 mL) was left for 15 h at rt. The mixture was poured into ice-water and the suspension was stirred for 2 h. The brown pale precipitate was filtered, washed with water and recrystallized from ethanol to afford compound (**16**) as a yellow pale solid (143 mg, 64%), mp 168-169 °C; IR: 1723, 1525, 1358, 1320; ^{1}H NMR (300 MHz): δ 2.56 (s, 3H, COMe), 7.40-8.40 (m, 8H, Ar-H); ^{13}C NMR (75 MHz): δ 26.1, 114.6, 120.5, 124.6, 124.8, 125.6, 128.7, 130.9, 131.8, 132.4, 133.9, 142.9, 147.5, 149.6, 168.3. *Anal.* Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.01; H, 4.10; N, 14.97

Reaction of benzimidazol (16) with iron A suspension of **16** (453 mg, 1.61 mmol) and powder iron (1.2 g, 21.42 mmol) in acetic acid-ethanol-water (60 mL, 1:1:1 v/v) was heated at 50-60°C with stirring for 1 h. Then the mixture was diluted with water (25 mL) and neutralized with sodium hydrogencarbonate, and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over sodium sulfate and evaporated *in vacuo* to give a white pale solid. Purification by column cromatography using (chloroform-ethyl acetate = 1:1) followed by recrystallization from ethanol afforded compounds (**19**) and (**20**).

6-Methylbenzoimidazo[1,2-c]quinazoline (**19**) (184 mg, 46 %); white powder mp 180-181 °C; IR: 1627, 1599, 1534; ^{1}H NMR (300 MHz): δ 3.17 (s, 3H, Me), 7.40-8.60 (m, 8H, Ar-H); ^{13}C NMR (75 MHz): δ 24.24, 115.77, 118.20, 119.96, 123.44, 124.17, 125.84, 127.67, 128.08, 129.90, 132.34, 142.54, 144.39, 147.49, 149.22; EIMS *m /e* (%): 233 (M^+, 100), 207 (41), 164 (36); *Anal.* Calcd for $C_{15}H_{11}N_3$: C, 77.22; H, 4.76; N, 18.02. Found: C, 76.90; H, 5.01; N, 18.02. *2-(1H-Benzimidazo-2-yl)acetanilide* (**20**) (120 mg, 32 %), white needles mp 204-205 °C; IR: 3237, 1672, 1630, 1587, 1547; ^{1}H NMR (300 MHz): δ 2.26 (s, 3H, Me), 7.20-8.80 (m, 8H, Ar-H), 13.03 (s, 1H, NH), 13.15 (s, 1H, NH); ^{13}C NMR (75 MHz): δ 25.75, 112.02, 115.73, 119.24, 120.34, 122.81, 123.26, 123.99, 127.82, 131.18, 134.02, 138.91, 142.60, 151.40, 169.00; EIMS *m /e* (%): 251 (M^+, 55), 236 (100), 233 (71), 209 (74); *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 71.68 , H, 5.22; N, 16.73. Found: C, 70.54; H, 5.28; N, 16.50.

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