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Synthesis of condensed quinolines and quinazolines as DNA ligands

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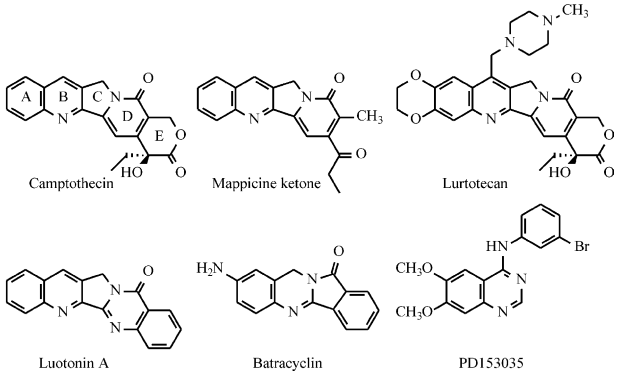
Abstract—Among new condensed quinolines and quinazolines the design of which were inspired by anti-cancer DNA-binding alkaloids such as camptothecin and batracyclin, DNA binding tests identify the 8-methoxy-7-piperazinylpropoxyindeno[1,2-*b*]quinolin-11-one tetracyclic system as a new motif for DNA recognition.

1. Introduction

The quinoline ring is frequently condensed with various heterocycles in the skeleton of the numerous natural alkaloids acting as DNA ligands and potentially useful as anti-cancer drugs. This is the case for several plant alkaloids such as camptothecin (CPT), isolated from *Camptotheca acuminata*,[1] a powerful antitumor agent targeting DNA topoisomerase I. The indolizino[1,2-*b*]quinoline CPT scaffold represented by the A–D rings provides the necessary framework for DNA interaction whereas the lactone E-ring interacts essentially, if not exclusively, with the active site of topoisomerase I.[2] This is also the case for mappicine ketone[3] (MPK), an analogue of mappicine isolated from *Mappia foetidia Miers*, identified as an antiviral agent acting at the DNA level.[4,5] We have recently developed a strategy which consists in eliminating the lactone E-ring of camptothecin, therefore prohibiting the targeting of topoisomerase I, but exploiting the indolizino[1,2-*b*]quinoline structure to design DNA sequence reading molecules.[6] On the other hand, the quinazoline ring has often been found in the structure of anti-cancer DNA-binding agents, such as luotonin A[7] or batracyclin,[8] or in the structure of anti-cancer tyrosine-kinase inhibitors such as PD153035.[9] We have extensively studied this family of compounds[10,11] and demonstrated that a slight modification in structure (methylation of the anilino group for example) could considerably reinforce the DNA-intercalating capacities of these small molecules.[12]



Moreover, the observation that the presence of alkoxy groups in *ortho*-position on the benzo group of quinoline[13] could provide specific cytoxicity on the human prostate carcinoma PC3 cell line[14] confirmed the importance of such catechol groups found in other chemical families[6,10,11,15] including camptothecin derivatives such as lurtotecan.[16]

Keywords: Quinolines; Quinazolines; DNA ligands.
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On the basis of these three sets of considerations, we propose (i) the design of new condensed quinolines obtained by a Friedländer-type reaction between an aminobenzaldehyde (or aminoacetophenone) substituted by a methoxy and an alkoxy (or aminoalkoxy) group and a cyclic ketone and (ii) the design of dialkoxyquinazolines built from the same starting materials (Fig. 1).

2. Results and discussion

2.1. Chemistry

2.1.1. 2-Amino- benzaldehydes 8a–c and acetophenones 9a–c (A). The synthesis of the required 2-aminobenzaldehydes **8a–c** and 2-aminoacetophenones **9a–c** was to be obtained by reducing the corresponding nitro compounds. Whatever the reaction conditions used, nitration of aldehyde **1** unexpectedly led to the corresponding 3-nitrobenzaldehyde **2** (Scheme 1), as proven by a HBMC proton–carbon correlation study (Fig. 2).

It was therefore anticipated that substitution of the hydroxy phenol group would induce electrophilic substitution in *ortho*-position of the carbonyl function, as previously indicated.[17,18]

Reaction of 3-dialkylaminopropyl chlorides R_2Cl (R_2 = **a**,**b**) with phenols **1** and **3** (Scheme 2) easily produced aryl ethers **4a**,**b** and **5a**,**b** whose nitration gave good to moderate yields of compounds **6a**,**b** and **7a**,**b**. NMR correlation studies (ROESY and HBMC) on **6a** and **7a** confirmed the ortho position of the nitro group relative to the carbonyl group (Fig. 3).

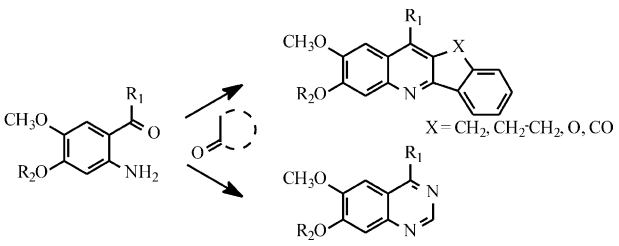
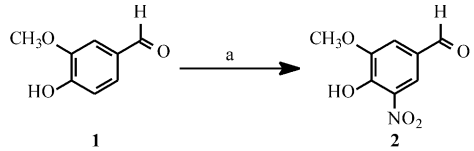


Figure 1. Design of condensed quinolines and quinazolines.



Scheme 1. Reagents and conditions: (a) HNO_3, CH_2Cl_2, −50 °C.

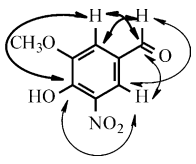


Figure 2. Main HBMC correlations for phenol **2**.

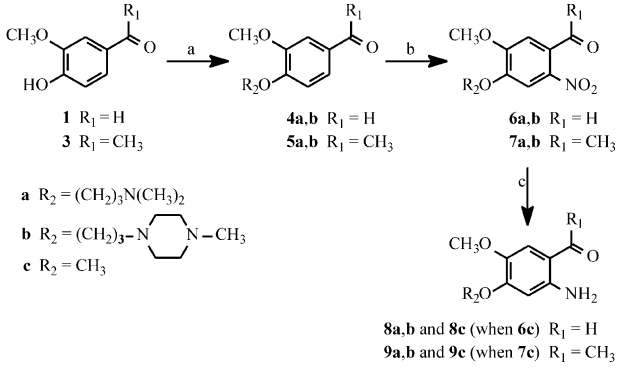
Reduction of **6a**,**b**, **7a**,**b** as well as commercial benzaldehyde **6c** and acetophenone **7c** was selective, according to a method already published (Fe/HCl);[19] the crude amines **8a–c** and **9a–c** were obtained at a very high yield and used as such in the next step, due to their instability.

2.1.2. 5,6-Dihydrobenzo[*a*] or [*c*]acridines 11c, 13b,c, 15b,c (B). Although the synthesis of the tetramethoxy dihydrobenzoacridine **15c** has already been performed by heating the hydrochloride of acetophenone **9c** with tetralone **14** at 140 °C in a sealed vessel,[20] we chose to perform the Friedländer cyclisations (Scheme 3) between *o*.carbonylanilines **9b**,**c** and the tetralones **10**, **12**, **14** in acidic medium (acetic acid).

While α-tetralones **12** and **14** resulted in dihydrobenzo[*c*]acridines **13** and **15**, β-tetralone **10** gave a very good yield of the single dihydrobenzo[*a*]acridine **11**. The poor yields corresponding to aminopropoxy benzo[*c*]acridines **13b** and **15b** are explained by their degradation on silica gel and required purification by chromatography on alumina.

2.1.3. 11*H*-indeno[1,2-*b*]quinolines 17b,c and their analogues 19b,c, 21a–c, 22a–c (C). These fused quinolines were obtained following the same procedure, from *o*.carbonylanilines **8a–c**, **9a–c** and 1-indanone **16** or its analogues **18**, **20** leading to the condensed tetracycles **17**, **19**, **21** (**21c**[21]), **22** (Scheme 4).

As for the aminoalkoxy heterocycles **13b** and **15b**, their analogues **17b**, **19b**, **21a**,**b**, **22a**,**b** were obtained at very low yields. It is also interesting to compare the yields of the homologous compounds **17c** (37%) and **13c** (71%) which reflect the lower reactivity of indanones vs. tetralones, as



Scheme 2. Reagents and conditions: (a) R_2Cl, K_2CO_3, DMF; (b) HNO_3 68%, $T < 10$ °C, 1 h; (c) Fe/HCl, AcOH/EtOH, reflux, 1 h.

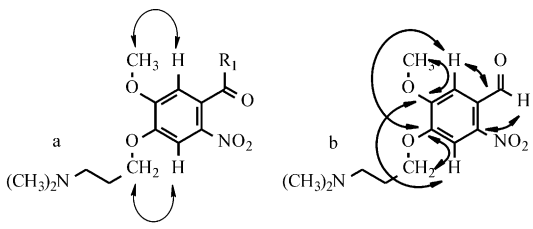
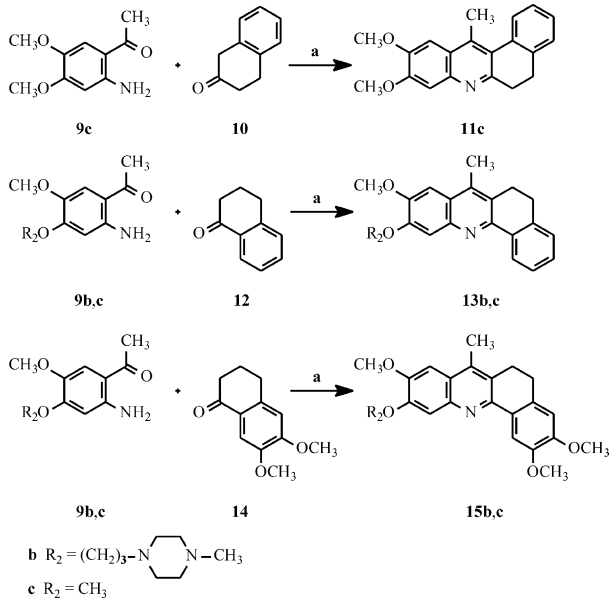
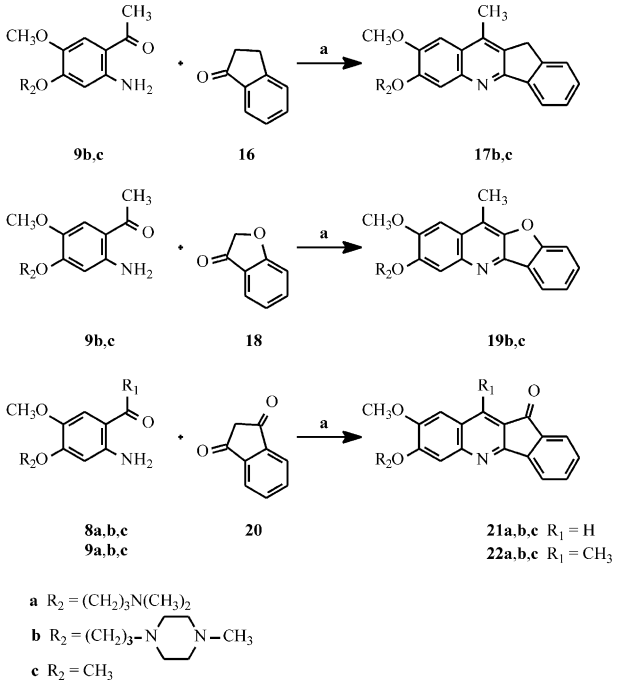


Figure 3. Main ROESY correlations (a) for **6a**, **7a** and (b) HBMC correlations for **6a**.

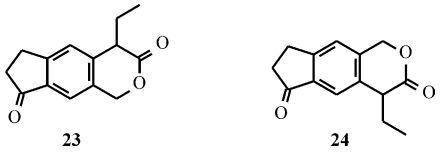


Scheme 3. Reagents and conditions: (a) AcOH, reflux, 2 h.

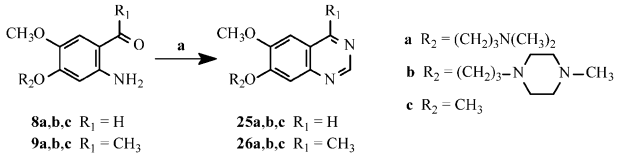


Scheme 4. Reagents and conditions: (a) AcOH, reflux, 2 h.

already observed[22] for the Friedländer reaction of indanones **23** and **24**.



2.1.4. Quinazolines 25a–c, 26a–c (D). With the same starting materials **8a–c**, **9a–c** and following the described method,[23] quinazolines **25** and **26** were easily obtained by reaction with formamide (Scheme 5) whereas **26c** has previously been obtained[24] by heating an ethanolic



Scheme 5. Reagents and conditions: (a) $HCONH_2$, AcOH, 2 h.

Table 1. DNA binding properties

Compd	K_{app} (10^6 M^{-1})[a]	ΔT_m (°C)[b]
17b	0.22±0.03	1.5
21a	4.25±0.07	5.8
21b	2.25±0.06	6.8
22a	1.91±0.06	2.9
22b	5.26±0.08	10.9
PD153035	nd[c]	0.6[d]

[a] Apparent binding constant measured by fluorescence ($n=3$).
[b] Variation of the ΔT_m ($T_{m\ drug–DNA\ complex} - T_{m\ DNA\ alone}$) of the complexes between DNA and the test compounds.
[c] Not determined.
[d] From ref 12.

ammonia solution of formanilide in a stainless steel bomb at 140 °C (82% yield).

2.2. Biological evaluation

All compounds were evaluated for DNA binding with two pharmacological tests using calf thymus DNA. A fluorescence assay was applied to determine binding constants and the results were compared to melting temperature measurements which can give information on the relative binding affinities of the compounds for any given DNA. Most compounds showed little interaction with DNA and their affinity was too low to be precisely calculated. In contrast, five compounds, **17b**, **21a**,**b**, **22a**,**b** as listed in Table 1, were found to compete with ethidium bromide for DNA binding and induced more or less pronounced stabilization of the duplex structure of DNA, as judged from the *T*m analysis.

For clarity, only data for these five compounds with $K_{app} > 10^4$ M^{-1} and $\Delta T_m > 1$ °C is reported here. The K_{app} values of other compounds were between 0.05 10^4 M^{-1} and 0.7×10^4 M^{-1}. A relative agreement was observed between the two assays, T_m and fluorescence quenching, used to monitor drug–DNA interaction. Slight differences were observed and are probably accounted for by varying experimental conditions (heating vs competition). Compound **22b** with a piperazinyl side chain was found to bind most tightly to DNA whereas the analogue **22a** with a dimethylamino chain was 3–4 times less potent in terms of DNA binding. The effect is clearly superior to that of the reference compounds PD153035 and CPT which both exhibit little interaction with DNA. Surprisingly, the same difference was not observed with the unmethylated analogues **21a**,**b**. Although no precise structure–DNA binding relationships could be delineated, it was interesting to observe that dialkoxyquinazolines **25a**,**b**,**c** and **26a**,**b**,**c** appeared to show little interaction with DNA, in contrast to our expectation on the basis of previous observations with related quinazoline derivatives.[12]

3. Conclusion

The results identify the indeno[1,2-*b*]quinolin-11-one tetracyclic ring system as a new motif for DNA recognition and support our recent finding that the A–D motif of the antitumor drug camptothecin offers a DNA binding element. Synthetic efforts are now directed towards substitution of the anilino group to increase DNA binding capacity (and possibly to restore kinase inhibitory activity) by analogy with previously studied anilinoquinazolines.[11]

4. Experimental

4.1. Chemistry

Melting points were determined on a Büchi 535 capillary melting point apparatus and remain uncorrected. Thin layer chromatography was performed on precoated Kieselgel 60F_{254} plates (Merck) and column chromatography on silica gel 60 230-400 mesh ASTM (Merck) or activated neutral alumina 50–160 μm (Prolabo). The IR spectra were recorded on a Bruker Vector 22 spectrophotometer and the NMR spectra on a Bruker AC 300P or a Bruker DPX 300 AVANCE at 300 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Service Central d'Analyses (CNRS, Vernaison, France).

4.1.1. 4-Hydroxy-3-methoxy-5-nitrobenzaldehyde (2). A solution of aldehyde **1** (1 g, 6.6 mmol) in CH_2Cl_2 (60 mL) was cooled to −50 °C; then fuming HNO_3 (d = 1.49, 7.7 mL, 185 mmol) was added dropwise. After stirring at −50 °C for 1 h, the reaction was quenched onto ice. The precipitated solid was filtered, washed with Et_2O and recrystallized from AcOEt to give a 60% yield of nitrophenol **2**; mp 80–81 °C; TLC R_f [AcOEt] = 0.6; IR (KBr) ν 3205, 1680, 1545, 1335 cm^{-1}; ^1H NMR (DMSO-d_6): 3.96 (3H, s), 7.62 (1H, s), 8.11 (1H, s), 9.87 (1H, s), 11.60 (1H, exchangeable).

4.1.2. 3-Methoxy-4-[3-(4-methyl-1-piperazinyl)propoxy] benzaldehyde dihydrochloride (4b). A stirred mixture of phenol **1** (10 g, 66 mmol), 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride (16.4 g, 66 mmol) and K_2CO_3 (36.3 g, 264 mmol) in DMF (80 mL) was heated at 80 °C for 4 h, then at room temperature for 48 h. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2. The organic phases were dried ($MgSO_4$) and Et_2O (200 mL) was added to the residue obtained after evaporation. The solid obtained on addition of a saturated Et_2O solution of HCl was recrystallized from 2-propanol, giving a 55% yield of **4b**; mp 197–198 °C; TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; IR (KBr) ν 1675 cm^{-1}; ^1H NMR (DMSO-d_6): 2.26 (2H, m), 2.83 (3H, s), 3.20–3.80 (10H, m), 3.85 (3H, s), 4.20 (2H, m), 7.20 (1H, d, *J* = 8.2 Hz), 7.42 (1H, s), 7.57 (1H, d, *J* = 8.2 Hz), 9.86 (1H, s), 12.10 (2H, s, exchangeable).

Amines **4a**, **5a**, **5b** were prepared in a similar way.

4.1.3. 4a (hydrochloride). 61% yield; mp 83–84 °C (toluene); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; IR (KBr) ν 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 2.45 (2H, m), 2.86 (6H, s), 3.29 (2H, t, *J* = 7.8 Hz), 3.88 (3H, s), 4.22 (2H, t, *J* = 5.7 Hz), 6.96 (1H, d, *J* = 8.2 Hz), 7.37 (1H, d, *J* = 1.6 Hz), 7.42 (1H, dd, *J* = 8.2, 1.6 Hz), 9.82 (1H, s).

4.1.4. 5a (hydrochloride). 60% yield; mp 177–178 °C (EtOH); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.6; IR (KBr) ν 1665 cm^{-1}; ^1H NMR (DMSO-d_6): 2.20 (2H, m), 2.53 (3H, s), 2.76 (6H, s), 3.19 (2H, t, *J* = 7.6 Hz), 3.82 (3H, s), 4.15 (2H, t, *J* = 6.1 Hz), 7.08 (1H, d, *J* = 8.3 Hz), 7.45 (1H, s), 7.61 (1H, d, *J* = 8.3 Hz), 11.03 (1H, s, exchangeable).

4.1.5. 5b (dihydrochloride). 59% yield; mp 217–218 °C (EtOH); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.4; IR (KBr) ν 1670 cm^{-1}; ^1H NMR (DMSO-d_6): 2.24 (2H, m), 2.54 (3H, s), 2.84 (3H, s), 3.18–3.80 (10H, m), 3.84 (3H, s), 4.18 (2H, t, *J* = 6.0 Hz), 7.11 (1H, d, *J* = 8.3 Hz), 7.47 (1H, s), 7.65 (1H, d, *J* = 8.3 Hz), 12.05 (2H, s, exchangeable).

4.1.6. 5-Methoxy-4-[3-(4-methyl-1-piperazinyl)propoxy]-2-nitrobenzaldehyde (6b). Compound **4b** (4 g, 11 mmol) was added portion by portion to cooled (0–5 °C) HNO_3 (d = 1.41, 22.3 mL, 506 mmol). The mixture was stirred for 1 h at a temperature below 10 °C. H_2O (50 mL), then K_2CO_3 were added and the solution was extracted with CH_2Cl_2. The organic phase was evaporated after drying ($MgSO_4$) and the residue was recrystallized from *i*Pr_2O, leading to a 55% yield of **6b**; mp 60–61 °C; TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.6; IR (KBr) ν 1680, 1525, 1325 cm^{-1}; ^1H NMR ($CDCl_3$): 2.11 (2H, m), 2.67–3.08 (13H, m), 4.01 (3H, s), 4.24 (2H, t, *J* = 6.2 Hz), 7.42 (1H, s), 7.64 (1H, s), 10.45 (1H, s).

Amines **6a**, **7a** and **7b** were prepared in a similar way.

4.1.7. 6a. 66% yield; mp 67–68 °C (*i*Pr_2O); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.6; IR (KBr) ν 1680, 1525, 1340 cm^{-1}; ^1H NMR ($CDCl_3$): 2.07 (2H, m, *J* = 6.9, 6.6 Hz), 2.26 (6H, s), 2.47 (2H, t, *J* = 6.9 Hz), 4.01 (3H, s), 4.23 (2H, t, *J* = 6.6 Hz), 7.41 (1H, s), 7.66 (1H, s), 10.44 (1H, s).

4.1.8. 7a. 57% yield; mp 90–91 °C (petroleum ether); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.7; IR (KBr) ν 1700, 1520, 1330 cm^{-1}; ^1H NMR ($CDCl_3$): 2.05 (2H, m, *J* = 7.1, 6.6 Hz), 2.26 (6H, s), 2.47 (2H, t, *J* = 7.1 Hz), 2.50 (3H, s), 3.97 (3H, s), 4.18 (2H, t, *J* = 6.6 Hz), 6.75 (1H, s), 7.66 (1H, s).

4.1.9. 7b. 51% yield; mp 85–86 °C (petroleum ether); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; IR (KBr) ν 1710, 1520, 1325 cm^{-1}; ^1H NMR ($CDCl_3$): 2.01 (2H, m), 2.64–3.01 (13H, m), 3.98 (3H, s), 4.23 (2H, t, *J* = 6.8 Hz), 7.47 (1H, s), 7.76 (1H, s).

4.1.10. 2-Amino-5-methoxy-4-[3-(4-methyl-1-piperazinyl) propoxy]benzaldehyde (8b). Fe (1 g, 17.4 mmol), then HCl (0.5 mL) were added to a stirred solution of nitro compound **6b** (1 g, 2.9 mmol) in a mixture of AcOH

(12.5 mL), EtOH (12.5 mL) and H_2O (6.36 mL). After refluxing for 1 h, the mixture was filtered on Celite, H_2O (50 mL), then K_2CO_3 were added. The solution was extracted with CH_2Cl_2 and the organic phases were dried ($MgSO_4$). The aminobenzaldehyde **8b** thus obtained was immediately used for the following Friedländer reaction.

Amines **8a**,**c** and **9a**,**b**,**c** were prepared in a similar way.

4.1.11. 9,10-Dimethoxy-7-methyl-5,6-dihydrobenzo[*c*]-acridine (13c). A solution of aminoketone **9c** (1 g, 5.1 mmol) in AcOH (3 mL) was added to a refluxing solution of tetralone **12** (0.76 g, 5.6 mmol) in glacial AcOH (2 mL). The mixture was refluxed for 2 h then cooled. The solid was collected then washed with Et_2O and the residue was chromatographed on alumina [CH_2Cl_2/MeOH (9.9:0.1)] and recrystallized from CH_2Cl_2, giving a 71% yield of **13c**; mp 211–212 °C; TLC R_f [CH_2Cl_2/CH_3OH (9:1)] = 0.9; ^{1}H NMR ($CDCl_3$): 2.61 (3H, s), 2.98–3.09 (4H, m), 3.98 (3H, s), 4.20 (3H, s), 7.16 (1H, s), 7.25–7.42 (3H, m), 7.48 (1H, s), 8.48 (1H, d, J = 7.2 Hz). Anal. calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.41; H, 6.26; N, 4.76.

Acridine **15c** was prepared in a similar way.

4.1.12. 15c. 85% yield; mp 227–228 °C (CH_2Cl_2) (lit.[20] 240 °C); TLC R_f [AcOEt] = 0.7; ^{1}H NMR ($CDCl_3$): 2.61 (3H, s), 2.92–3.10 (4H, m), 3.95–4.12 (12H, m), 6.76 (1H, s), 7.17 (1H, s), 7.51 (1H, s), 8.07 (1H, s). Anal. calcd for $C_{22}H_{23}NO_4 \cdot H_2O$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.62; H, 6.21; N, 3.92.

4.1.13. 8-Methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-11*H*-indeno[1,2-*b*]quinolin-11-one (21b). A solution of aminobenzaldehyde **8b** (1 g, 3.2 mmol) in AcOH (3 mL) was added to a refluxing solution of indanedione **20** (0.5 g, 3.5 mmol) in glacial AcOH (2 mL). The mixture was refluxed for 2 h and the solvent was evaporated. The residue was chromatographed on alumina [CH_2Cl_2/MeOH (9.9:0.1)] and recrystallized from Et_2O, giving a 25% yield of **21b**; mp 171–172 °C; TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; ^{1}H NMR ($CDCl_3$): 2.15 (2H, m), 2.30 (3H, s), 2.44–2.68 (10H, m), 3.99 (3H, s), 4.28 (2H, t, J = 6.4 Hz), 7.07–8.17 (7H, m). Anal. calcd for $C_{25}H_{27}N_3O_3 \cdot H_2O$: C, 68.95; H, 6.71; N, 9.65. Found: C, 68.54; H, 6.52; N, 9.41.

Quinolines **11c**, **13b**, **15b**, **17b**,**c** and **19b**,**c** were prepared in a similar way.

4.1.14. 11c. 92% yield; mp 163–164 °C (cyclohexane); TLC R_f [AcOEt/cyclohexane (1:1)] = 0.2; ^{1}H NMR ($CDCl_3$): 2.87 (3H, s), 2.93–3.13 (4H, m), 4.04 (3H, s), 4.05 (3H, s), 7.24–7.58 (6H, m). Anal. calcd for $C_{20}H_{19}NO_2 \cdot H_2O$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.52; H, 6.41; N, 4.63.

4.1.15. 13b. 17% yield; mp 159–160 °C (CH_2Cl_2); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.6; ^{1}H NMR ($CDCl_3$): 2.14 (2H, m), 2.32 (3H, s), 2.42–2.72 (13H, m), 2.99–3.10 (4H, m), 4.03 (3H, s), 4.28 (2H, t, J = 6.9 Hz), 7.17 (1H, s), 7.25–7.43 (3H, m), 7.49 (1H, s), 8.47 (1H, d, J = 6.5 Hz). Anal. calcd for $C_{27}H_{33}N_3O_2 \cdot 2.5H_2O$: C, 68.04; H, 8.04; N, 8.82. Found: C, 68.26; H, 8.01; N, 8.91.

4.1.16. 15b. 11% yield; mp 192–193 °C (CH_2Cl_2); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; ^{1}H NMR ($CDCl_3$): 2.16 (2H, m), 2.31 (3H, s), 2.42–2.68 (13H, m), 2.92–3.10 (4H, m), 3.95–4.07 (9H, m), 4.28 (2H, t, J = 6.9 Hz), 6.76 (1H, s), 7.17 (1H, s), 7.45 (1H, s), 8.05 (1H, s). Anal. calcd for $C_{29}H_{37}N_3O_4 \cdot H_2O$: C, 68.35; H, 7.71; N, 8.24. Found: C, 68.76; H, 7.48; N, 8.45.

4.1.17. 17b. 14% yield; mp 176–178 °C (CH_2Cl_2); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; ^{1}H NMR ($CDCl_3$): 2.15 (2H, m), 2.31 (3H, s), 2.40–2.71 (13H, m), 3.96 (2H, s), 4.04 (3H, s), 4.30 (2H, t, J = 6.9 Hz), 7.22–8.22 (6H, m). Anal. calcd for $C_{26}H_{31}N_3O_2 \cdot 1.5H_2O$: C, 70.24; H, 7.71; N, 9.45. Found: C, 70.48; H, 7.40; N, 9.55.

4.1.18. 17c. 37% yield; mp 210–211 °C (CH_2Cl_2); TLC R_f [CH_2Cl_2/CH_3OH (9:1)] = 0.8; ^{1}H NMR ($CDCl_3$): 2.64 (3H, s), 3.87 (2H, s), 4.04 (3H, s), 4.06 (3H, s), 7.15–8.24 (6H, m). Anal. calcd for $C_{19}H_{17}NO_2 \cdot H_2O$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.81; H, 5.89; N, 4.49.

4.1.19. 19b. 14% yield; mp 174–175 °C (CH_2Cl_2); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; ^{1}H NMR ($CDCl_3$): 2.16 (2H, m), 2.31 (3H, s), 2.40–2.88 (13H, m), 4.10 (3H, s), 4.30 (2H, t, J = 6.9 Hz), 7.25–8.32 (6H, m). Anal. calcd for $C_{25}H_{29}N_3O_3 \cdot H_2O$: C, 68.33; H, 7.14; N, 9.60. Found: C, 68.19; H, 6.87; N, 9.97.

4.1.20. 19c. 27% yield; mp 204–205 °C (CH_2Cl_2); TLC R_f [AcOEt] = 0.9; ^{1}H NMR ($CDCl_3$): 2.87 (3H, s), 4.06 (3H, s), 4.11 (3H, s), 7.24–8.34 (6H, m). Anal. calcd for $C_{18}H_{15}NO_3 \cdot 1.5H_2O$: C, 67.49; H, 5.66; N, 4.37. Found: C, 67.10; H, 5.27; N, 4.09.

4.1.21. 7,8-Dimethoxy-11*H*-indeno[1,2-*b*]quinolin-11-one (21c). A solution of aminobenzaldehyde **8c** (1 g, 5.5 mmol) in AcOH (3 mL) was added to a refluxing solution of indanedione **20** (0.9 g, 6.1 mmol) in AcOH (2 mL). The mixture was refluxed for 2 h, then the solvent was evaporated. The residue was collected and washed with AcOEt before the solid was chromatographed on alumina [CH_2Cl_2/MeOH (9.9:0.1)] and recrystallized from toluene, giving a 43% yield of **21c**; mp 260 °C (lit.[21] 287 °C); TLC R_f [CH_2Cl_2/MeOH (9.9:0.1)] = 0.1 (lit.[21] ($CHCl_3$) 0.24); ^{1}H NMR ($CDCl_3$): 4.05 (3H, s), 4.08 (3H, s), 7.11–8.21 (7H, m). Anal. calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.24; H, 4.44; N, 4.72.

Quinolines **21a** and **22a**–**c** were prepared in a similar way.

4.1.22. 21a. 47% yield; mp 146–147 °C (Et_2O); TLC R_f [CH_2Cl_2/CH_3OH/NH_4OH (90:8:2)] = 0.5; ^{1}H NMR ($CDCl_3$): 2.10 (2H, m, J = 7.2, 6.8 Hz), 2.28 (6H, s), 2.52 (2H, t, J = 7.2 Hz), 4.00 (3H, s), 4.27 (2H, t, J = 6.8 Hz), 7.07–7.17 (7H, m). Anal. calcd for $C_{27}H_{22}N_2O_3 \cdot 0.5H_2O$:

C, 71.14; H, 6.24; N, 7.54. Found: C, 71.65; H, 6.08; N, 7.17.

4.1.23. 22a. 38% yield; mp 143–144 °C (Et_2O); TLC R_f [CH_2Cl_2/CH_3OH (9.9:0.1)] = 0.6; ^1H NMR ($CDCl_3$): 2.15 (2H, m, J = 7.2, 6.8 Hz), 2.28 (6H, s), 2.53 (2H, t, J = 7.2 Hz), 2.96 (3H, s), 4.01 (3H, s), 4.27 (2H, t, J = 6.8 Hz), 7.22–7.95 (6H, m). Anal. calcd for $C_{23}H_{24}N_2O_3 \cdot H_2O$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.28; H, 6.55; N, 7.22.

4.1.24. 22b. 18% yield; mp 167–168 °C (Et_2O); TLC R_f [CH_2Cl_2/CH_3OH (9.9:0.1)] = 0.6; ^1H NMR ($CDCl_3$): 2.10 (2H, m), 2.30 (3H, s), 2.42–2.93 (13H, m), 3.99 (3H, s), 4.26 (2H, t, J = 6.4 Hz), 7.19–7.93 (6H, m). Anal. calcd for $C_{26}H_{29}N_3O_3 \cdot H_2O$: C, 69.47; H, 6.95; N, 9.35. Found: C, 70.04; H, 6.69; N, 9.02.

4.1.25. 22c. 51% yield; mp >260 °C (AcOEt); TLC R_f [CH_2Cl_2/CH_3OH (9.9:0.1)] = 0.1; ^1H NMR ($CDCl_3$): 2.98 (3H, s), 4.06 (3H, s), 4.07 (3H, s), 7.25–7.97 (6H, m). Anal. calcd for $C_{19}H_{15}NO_3 \cdot 0.25H_2O$: C, 73.65; H, 5.04; N, 4.52. Found: C, 73.43; H, 4.86; N, 4.20.

4.1.26. 6,7-Dimethoxyquinazoline oxalate (25c). A stirred mixture of aminobenzaldehyde **8c** (1 g, 5.5 mmol) and glacial AcOH (5.5 mL) in $HCONH_2$ (28 mL) was refluxed for 2 h, then cooled. H_2O (20 mL), then K_2CO_3 were added and the solution was extracted with CH_2Cl_2. After drying ($MgSO_4$), the organic phase was evaporated and the residue was chromatographed on alumina [CH_2Cl_2/MeOH (9.9:0.1)]. A solution of oxalic acid (2.08 g, 16.5 mmol) in AcOEt was added dropwise to an AcOEt solution of the crude residue resulting from chromatography and the precipitate was washed with Et_2O, then recrystallized from MeOH, giving a 81% yield of **25c**; mp 180–181 °C; TLC R_f [CH_2Cl_2/CH_3OH (9:1)] = 0.8; ^1H NMR (DMSO-d_6): 3.97 (3H, s), 3.99 (3H, s), 7.36–7.49 (2H, m), 9.07 (1H, s), 9.30 (1H, s). Anal. calcd for $C_{10}H_{10}N_2O_2 \cdot 1.5C_2H_2O_4$: C, 48.01; H, 4.03; N, 8.61. Found: C, 47.90; H, 4.23; N, 8.25.

Quinazolines **25a**,**b** and **26a**–**c** were prepared in a similar way.

4.1.27. 25a (dioxalate). 65% yield; mp 221–222 °C (MeOH); TLC R_f [CH_2Cl_2/MeOH (1:1)] = 0.1; ^1H NMR (DMSO-d_6): 2.22 (2H, m), 2.80 (6H, s), 3.22 (2H, m), 3.94 (3H, s), 4.28 (2H, m), 7.32–7.50 (2H, m), 9.03 (1H, s), 9.29 (1H, s). Anal. calcd for $C_{14}H_{19}N_3O_2 \cdot 2C_2H_2O_4$: C, 48.98; H, 5.25; N, 9.52. Found: C, 48.67; H, 4.86; N, 9.33.

4.1.28. 25b (dioxalate). 51% yield; mp 221–222 °C (MeOH); TLC R_f [CH_2Cl_2/MeOH (1:1)] = 0.1; ^1H NMR (DMSO-d_6): 2.03 (2H, m), 2.56 (3H, s), 2.63–2.78 (8H, m), 3.44 (2H, m), 3.96 (3H, s), 4.26 (2H, m), 7.35–7.51 (2H, m), 9.07 (1H, s), 9.30 (1H, s). Anal. calcd for $C_{17}H_{24}N_4O_2 \cdot 2.5C_2H_2O_4$: C, 48.80; H, 5.40; N, 10.35. Found: C, 47.97; H, 5.84; N, 10.00.

4.1.29. 26a (dioxalate). 70% yield; mp 176–177 °C (MeOH); TLC R_f [CH_2Cl_2/MeOH (1:1)] = 0.1; ^1H NMR (DMSO-d_6): 2.23 (2H, m), 2.75–2.85 (9H, m), 3.23 (2H, m), 3.99 (3H, s), 4.27 (2H, m), 7.35–7.45 (2H, m), 8.91 (1H, s). Anal. calcd for $C_{15}H_{21}N_3O_2 \cdot 2C_2H_2O_4$: C, 50.11; H, 5.53; N, 9.23. Found: C, 50.19; H, 5.99; N, 9.28.

4.1.30. 26b (trioxalate). 42% yield; mp 221–222 °C (MeOH); TLC R_f [CH_2Cl_2/MeOH (1:1)] = 0.1; ^1H NMR (DMSO-d_6): 2.01 (2H, m), 2.57 (3H, s), 2.60–2.69 (8H, m), 2.84 (3H, s), 3.44 (2H, m), 3.98 (3H, s), 4.24 (2H, m), 7.32–7.44 (2H, m), 8.90 (1H, s). Anal. calcd for $C_{18}H_{26}N_4O_2 \cdot 3C_2H_2O_4$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.18; H, 6.00; N, 9.32.

4.1.31. 26c (oxalate). 62% yield; mp 215–216 °C (MeCN); TLC R_f [CH_2Cl_2/MeOH (9.9:0.1)] = 0.7; ^1H NMR (DMSO-d_6): 2.81 (3H, s), 3.96–4.02 (6H, m), 7.29–7.38 (2H, m), 8.90 (1H, s). Anal. calcd for $C_{11}H_{12}N_2O_2 \cdot C_2H_2O_4$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.89; H, 4.89; N, 9.59.

4.2. DNA interaction studies

Binding constants were determined by fluorescence using a competitive displacement assay with DNA-bound ethidium. Fluorescence data was recorded at room temperature with a SPEX fluorometer Fluorolog. Excitation was at 515 nm and fluorescence emission was monitored over the range 550 to 700 nm. Experiments were performed with an [ethidium]/[DNA] molar ratio of 12.6:10 and a drug concentration range of 0.01–100 μM in BPE buffer at pH 7.1 (6 mM Na_2HPO_4, 2 mM NaH_2PO_4, 1 mM EDTA). C_{50} values for ethidium displacement were calculated using a fitting function incorporated into Prism 3.0 and the apparent equilibrium binding constants (K_{app}) were calculated as follows:

$$K_{app} = (1.26\ \mu M/C_{50}) \times K_{ethidium},$$
$$\text{with } K_{ethidium} = 10^7\ M^{-1}.$$

Melting temperature (T_m) measurements were performed in BPE buffer using 20 μM calf thymus DNA and 20 μM of test compound in 1 mL quartz cuvettes at 260 nm with a heating rate of 1 °C/min. The T_m values were obtained from first-derivative plots.

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