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2-(*N*-Methylanilino)-3-formylchromone—a versatile synthon for incorporation of chromone moiety in a variety of heterocyclic systems and macrocycles through reactions with bifunctional nucleophiles

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Abstract—Reactions of 2-(*N*-methylanilino)-3-formylchromones with a number of bifunctional nucleophiles, involving substitution of *N*-methylanilino moiety and/or condensations with 3-formyl function have provided an easy access to a variety of potentially biologically active hetero-annelated chromones, novel macrocycles, and tetradentate ligands having intact chromone moiety.

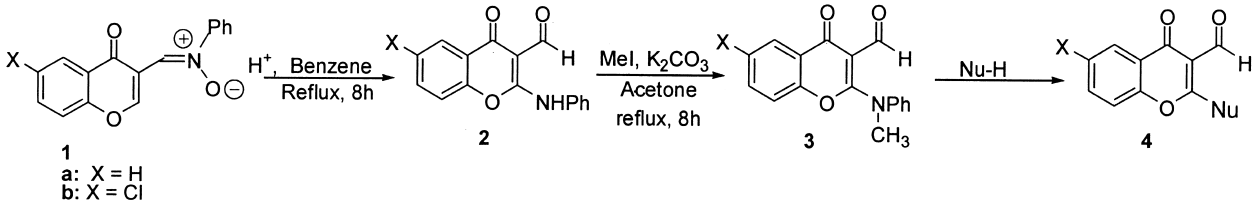
1. Introduction

The chromone moiety forms the important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin and many of them have useful medicinal applications.[1] Consequently, chromone chemistry continues to draw considerable interest of synthetic organic and medicinal chemists.[2] Though, 3-formylchromone has emerged as a valuable synthon for incorporation of the chromone moiety into a number of molecular frameworks,[3] its synthetic utility is limited due to facile opening of the chromone ring[3,4] and strategies are being developed to circumvent it.[5]

Recently, we have reported[6] a facile conversion of C-(4-oxo-4*H*[1]benzopyran3-yl)-*N*-phenylnitrones (**1**) to 2-(*N*-methylanilino)-3-formylchromones (**3**) and the latter's utilization, by easy displacement of its *N*-methylanilino moiety with a variety of nitrogen-nucleophiles, to obtain a number of chromano-heterocycles, and 2-alky/arylamino-chromones (Scheme 1); the latter are highly sought after on account of their valuable biological activities such as antiplatelet, antiproliferative and antidepressant.[7] Herein we describe the further utilization of 2-(*N*-methylanilino)-3-formylchromones through reactions with a number of bifunctional nucleophiles to obtain a variety of chromano-heterocycles, novel macrocycles having an intact chromone moiety at the periphery and some novel tetradentate ligands having an intact chromone moiety with potential applications as fluorescent sensors.

2. Results and discussion

Earlier[6] we had reported the reaction of **3b** with *o*-phenylenediamine leading to chromano-azepine (**5b**) in high yield. We have now carried out, besides the reaction of **3a** with *o*-phenylenediamine, the reactions of **3a**,**b** with



Scheme 1.

Keywords: chromones; addition–elimination; condensation; chromano-azepines; chromano-oxazepines; chromano-thiazapine; chromanopyrazoles; chromanopyrole; chromano-quinolines; macrocycles.

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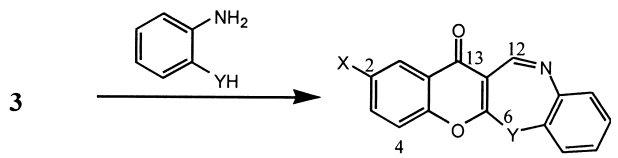


5
a: X = H, Y = NH
b: X = Cl, Y = NH
c: X = H, Y = O
d: X = Cl, Y = O
e: X = H, Y = S

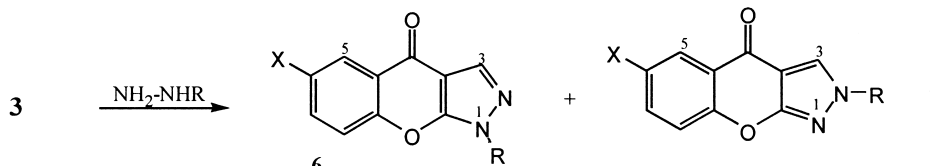
Scheme 2.

ortho-substituted anilines such as *o*-aminophenol, and *o*-amino-thiophenol, leading to chromano-heterocyclic systems (**5a**–**e**, Scheme 2). In the case of reaction with *o*-phenylenediamine, the best yield of diazepine (**5a**) was obtained when reaction was carried out in aqueous-acetonitrile (80:20). The use of anhydrous solvents led only to highly insoluble products, which could not be investigated further. The corresponding reactions with *o*-aminophenol and *o*-aminothiophenol were carried out in refluxing xylene and afforded chromano-oxazepines (**5c**,**d**), and chromano-thiazepine (**5e**), respectively, in high yields.

The structures have been arrived at by detailed spectroscopic analysis and comparison of the spectroscopic data with the data reported for related systems.[8] The C12–H in the ^{1}H NMR of oxazepine (**5c**) appeared at δ 8.89 (1H singlet) and C1–H as a broad doublet at δ 8.37; all other proton resonances were in the aromatic region. The ^{13}C NMR spectrum of **5c** revealed, inter alia, the C13 resonance at δ 172.81, which was in consonance with an intact chromone ring;[6] assigned structures are also corroborated by IR, microanalytical and mass spectral data.

We had reported earlier that reaction of 6-chloro-2-*N*-methylanilino-3-formylchromones (**3b**) with hydrazine-hydrate in aqueous-acetonitrile (80:20), affords chromano-pyrazole (**6a**, 45%).[6] Now the reactions of **3a**,**b** have been carried out with phenylhydrazine in refluxing dry aceto-nitrile leading to chromano-pyrazoles (**6b**,**c**), derived from an initial condensation of phenylhydrazine with the formyl group followed by nucleophilic substitution at C2. However, in the reaction of **3a** (X=H) with phenylhydrazine, another product (**6b′**) derived from initial substitution at C2 followed by condensation with the formyl group was also formed (Scheme 3). The structures of the products are again based on spectroscopic analysis. In the ^{1}H NMR of **6b** the C3–H appeared as a singlet at δ 8.58 and C5–H at δ 8.29 (dd, 1H), while in case of **6b′**, the C5–H appeared at δ 8.36 (dd, 1H) and C3–H at δ 8.25 (s, 1H); these structural conclusions are supported by a comparison of the NMR spectral data of **6b**, **6b′** and **6c** and corroborated by ^{13}C NMR as well as mass spectral data.

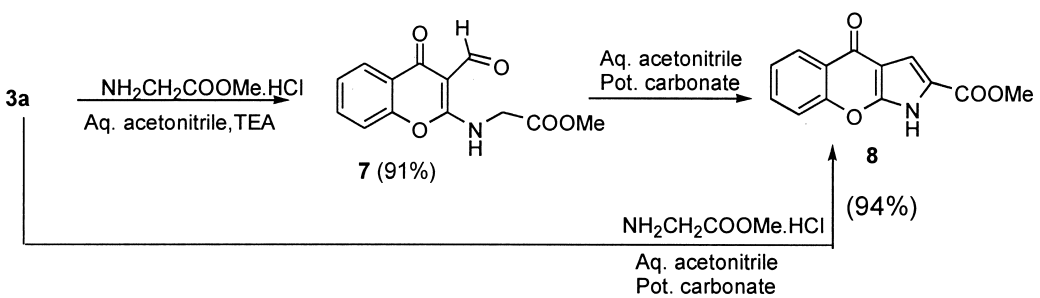
It has been reported[3h] that reaction of 3-formylchromone with ethyl glycinate affords products, which are derived from opening of the chromone ring. Presently, we have reacted **3a** with methyl glycinate-hydrochloride by refluxing in aqueous-acetonitrile, in the presence of triethylamine, which led to isolation of the C2 substituted product (**7**, Scheme 4) in 91% yield; the latter has been characterized spectroscopically. Its ^{1}H NMR revealed, inter alia, aldehydic proton resonance at δ 10.27 along with a 2H doublet at δ 4.37 and a 3H singlet at δ 3.87.[9] However, when potassium carbonate was used instead of triethylamine, the in situ formed **7** underwent intramolecular cyclization to chromano-pyrrole (**8**). Refluxing of **7** in aqueous-acetonitrile in the presence of potassium carbonate also led to formation of **8**. The structure of **8** has been assigned based on spectroscopic analyses. The characteristic features of its ^{1}H NMR spectrum being a broad singlet at δ 9.56 (C3–H) and a 3H singlet δ 3.75 ($-OCH_3$); the doublet at δ 4.37 observed in the case of **7**, disappears in the ^{1}H NMR spectrum of **8**. The mass spectrum of **8** was also in consonance with the assigned structure.



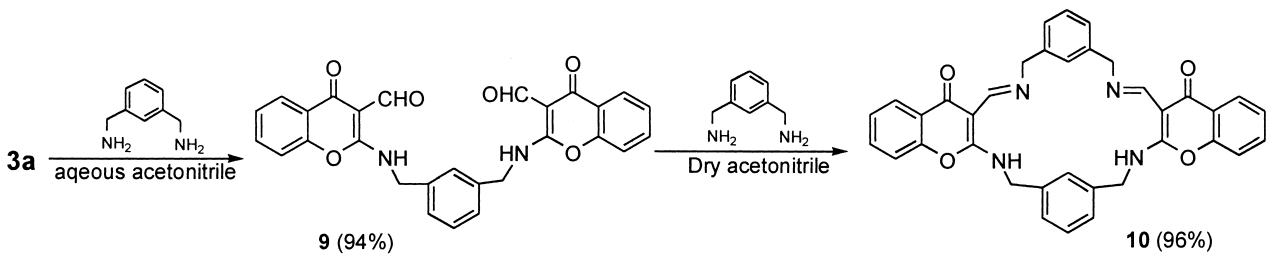
6
a: R = H, X = Cl (45%)
b: R = Ph, X=H (83%)
c: R = Ph, X = Cl (90%)

6b' (X=H, R=Ph, 12%)

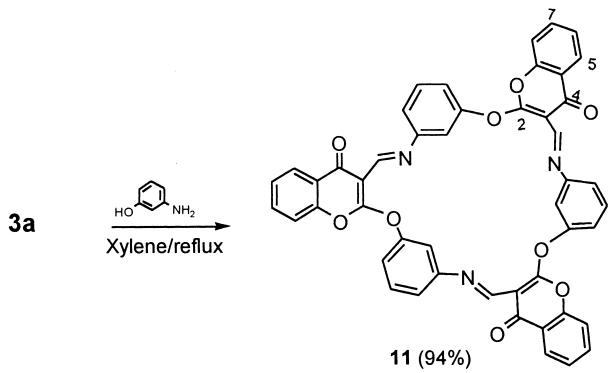
Scheme 3.



Scheme 4.



Scheme 5.



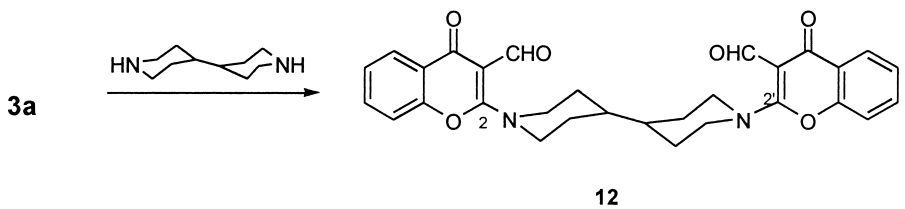
Scheme 6.

Recently, some interesting applications such as a receptor for hydroxycarboxylates have been reported for a chromone based macrocycle.[10] However, attempts at obtaining macrocycles by reacting 3-formylchromone with diamines had led to only ring-opened products.[3i] A lot of attention is being drawn towards the development of fluorescent metal sensors, mainly based on the common design that a modulation of fluorescence occurs whenever a fluorophore interacts directly with the nonbonding electrons of a metal-chelating group.[11] Therefore, a facile route to macrocycles involving a 2-amino/oxygen-substituted chromone moiety was a highly desired objective. Towards this end, it was decided to react **3** with α,ω-diamines. When equivalent amounts of **3a** and *m*-xylene-diamine were refluxed in dry-acetonitrile, the product obtained was a white solid having very low solubility. It appeared to be a 2+2 macrocycle from its FAB-mass and IR spectra; the latter did not reveal presence of a band due to a formyl group, anticipated around 1670–1690 cm^{-1}, however, its exact structure (head to head or head to tail) could not be established. Alternatively, when half molar equivalent of amine was refluxed with **3a** in aqueous-acetonitrile, the disubstituted product (**9**) with intact chromone moiety was obtained in high yield, which was characterized spectroscopically. Its ^1H NMR spectrum showed a broad singlet (2H) at δ 11.00 due to N–Hs and aldehydic proton resonances at δ 10.23 (bs, 2H). Appearance of C5–H at δ 8.22 as a broad doublet indicated that the chromone moiety is intact;[6] the FAB-mass spectrum $[(M+H)^+$ at *m/z* 481.3] also corroborated the structure. Compound **9** on treatment with one molar equivalent of *m*-xylene-diamine in dry-acetonitrile afforded the 2+2 'head to head' macrocycle (**10**, Scheme 5) in high yield, whose formation has been confirmed by FAB-mass spectrum through $(M+H)^+$ ion at 581.3.

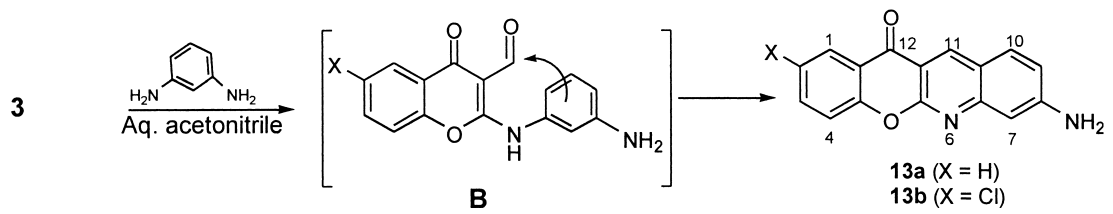
On the other hand reaction of **3a** with *m*-aminophenol in refluxing xylene led to 3+3-macrocycle (**11**) in high yield (Scheme 6). The formation of the macrocycle (**11**) has been established, inter alia, by FAB-mass spectrum $[(M+H)^+$ at 792.4) and comparison of NMR spectral data with that of **5c**,**d**.

As a variation, compound **3a** was reacted with dipiperidine-hydrochloride (half molar equivalent), by stirring in dry-acetonitrile at 70°C, in presence of anhydrous-potassium carbonate, which resulted in the disubstituted product (**12**, Scheme 7) in high yield (95%). The structure of **12** has been established spectroscopically. However, attempted condensation of **12** with aliphatic diamines such as 1,3-diamino-propane and 1,4-diaminobutane did not yield any macrocycle as nucleophilic substitution by amines at C2 predominated.

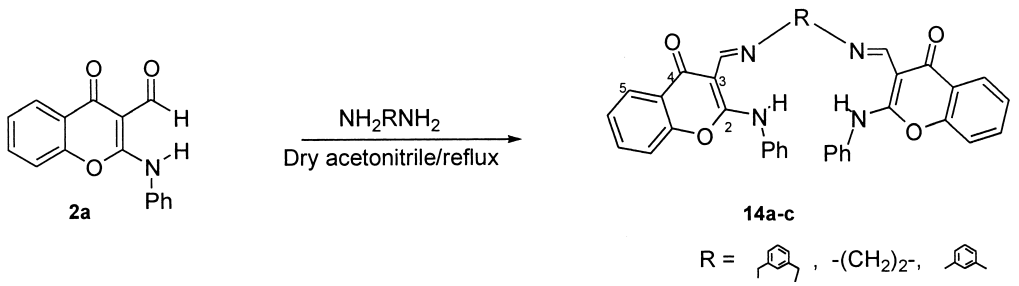
However, when *m*-phenylenediamine was reacted with **3a** by refluxing in xylene, it led to formation of only oligomeric materials and no characterizable product was isolated. On the contrary refluxing equimolar aqueous-acetonitrile (80:20) solutions of *m*-phenylenediamine and **3a**,**b** led to chromano-quinolines (**13a**,**b**) in good yield, which are derived from intramolecular cyclization of the C2 substituted intermediate (**B**, Scheme 8). The structures of **13a**,**b** have been established by detailed spectroscopic analysis. The ^1H NMR of **13b** revealed two singlets (1H each) at δ 9.03 and δ 7.08, three doublets (1H each) at δ 8.26, δ 7.84, and δ 7.54, and two (1H) double doublets (δ 7.67 and δ 6.99). The assigned structures are also supported by the respective mass spectra. It may be mentioned here that such chromano-tetracycles have been ascribed a number of useful biological activities.[12]



Scheme 7.



Scheme 8.



Scheme 9.

In addition to the macrocyclic fluorescent receptors, a number of non-cyclic fluorescent ligands based on the same general approach discussed above are also finding valuable application.[11] Presently, we have utilized **2a** to obtain non-cyclic ligands (**14**, Scheme 9) containing intact fluorescent chromone moiety. These have been characterized spectroscopically. The NH protons in these molecules (**14**) appear in the region δ 12–14 and it is anticipated that these NH groups will be deprotonated during complexation with metal ions. The 2-anilino moieties in **14** can be replaced by other arylamino or *sec*·amino groups[6] and this can be utilized to modulate the spectral properties of these ligands. The investigations on complexation of these ligands with metal ions are in progress and shall be reported elsewhere.

The reactions of 2-(*N*-methylanilino)-3-formylchromones with various bifunctional nucleophiles have, thus, provided an easy access to a large number potentially biological active heteroannulated-chromones and macrocycles having an intact chromone moiety at the periphery. The reaction with *m*-phenylenediamine, however, results in an amino-substituted chromanoquinoline and such chromane based polycyclic molecules are known to display useful biological activities.[12] Macrocycles as well as synthesized noncyclic ligands having intact fluorescent chromone moieties on the periphery can be useful as fluorescent sensors.

3. Experimental

3.1. General information

NMR spectra were recorded on Bruker 200 MHz FT NMR spectrometer, $CDCl_3$/DMSO-d_6/D_2O as solvents. Chemical shifts are reported in ppm as down field displacements from tetramethylsilane used as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP-2000A spectrometer. The microanalytical data were collected on a Perkin–Elmer 240C elemental analyzer. IR spectra were recorded on a Shimadzu DR 2001 IR spectrophotometer as pellets with KBr and are reported in wave numbers (cm^{-1}). All melting points are uncorrected and measures in open glass-capillaries. Column chromatography was conducted using silica gel 60–120 mesh (Acme, India). Solvents, starting materials and reagents were purchased from commercial suppliers and used after purification (crystallization/distillation). 3-Formylchromones were purchased from Aldrich and used as supplied.

3.1.1. 6*H*-[1]-Benzopyrano[2,3-*b*][1,5]-benzodiazepine-13-one (5a). 2-(*N*-Methylanilino)-3-formylchromone **3a** (279 mg, 1 mmol) was dissolved in refluxing aqueous-acetonitrile (80:20) and the solution of *o*-phenylenediamine (108 mg, 1 mmol) in acetonitrile (4 mL) added to it, and the contents were refluxed for 6 h and cooled. Yellow crystalline solid (**5a**), which separated out was filtered and washed with little acetonitrile and re-crystallized from hexane–$CHCl_3$ (3:1), (Yield 241 mg, 0.92 mmol, 92%), mp 268–269°C (hexane–$CHCl_3$ 3:1); λ_{max} (MeOH): 312.4, 285.8, 247 nm; ν_{max} (KBr): 3230 (b), 1642, 1626, 1581, 1533, 1461, 1404, 1378 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 11.78 (bs, 1H, NH), 9.33 (s, 1H, C12–H), 8.32 (bd, 1H, J=8.36 Hz, C1–H), 7.81–7.74 (m, 2H, arom-Hs), 7.62–7.49 (m, 3H, arom-Hs), 7.30–7.25 (m, 2H, arom-Hs); mass *m/z*: 263 (M^++1, 8), 262 (M^+, 26), 171 (86), 71 (100). Anal. calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68%; found: C, 73.65; H, 3.65; N, 10.81.

3.1.2. [1]Benzopyrano[2,3-*b*][1,5]-benzoxazepin-13-one (5c). A solution of 2-(*N*-methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) and *o*-aminophenol (109 mg, 1 mmol) in xylene (50 mL) was refluxed, and the progress of the reaction was monitored by tlc. After the completion of reaction (20 h), the solvent was evaporated under vacuum. Crystallization of the residue from acetonitrile (5 mL) afforded the title compound (**5c**, 234 mg, 0.89 mmol, 89%) as a reddish-crystalline solid, mp 140–41°C (hexane–$CHCl_3$ 3:1); λ_{max} (MeOH): 342, 306, 260 nm; ν_{max} (KBr): 1663, 1621, 1573, 1527, 1512, 1428, 1338, 1302, 1262, 1208, 1085, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.89 (s, 1H, C12–H), 8.37 (bd, 1H, J=7.56 Hz, C1–H), 7.77–7.69 (m, 2H, arom-Hs), 7.62–7.44 (m, 3H, arom-Hs),

7.36–7.24 (m, 2H, arom-Hs); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.81 (C13), 158.36 (C12), 157.53 (C5a), 155.66 (C4a), 150.39 (C6a), 141.20 (C10a), 134.14 (CH), 126.69 (CH), 126.16 (CH), 125.29 (CH), 124.66 (C13a), 124.56 (CH), 120.20 (CH), 118.11 (C4), 113.96 (C12a), 110.78 (CH); mass *m/z*: 264 (M^++1, 8), 263 (M^+, 40), 169 (70), 111 (44), 83 (49), 71 (100). Anal. calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N 5.32%; found: C, 72.79; H, 3.42; N, 5.41.

3.1.3. 2-Chloro-[1]benzopyrano[2,3-*b*][1,5]-benzoxazepin-13-one (5d). A solution of 6-chloro-2-(*N*-methylanilino)-3-formylchromone (**3b**, 313 mg, 1 mmol) and *o*-aminophenol (109 mg, 1 mmol) in xylene (50 mL) was refluxed for 20 h. Removal of solvent under vacuum and crystallization of the residue from acetonitrile afforded the title compound (**5d**, 270 mg, 0.91 mmol, ~91%) as a brownish-crystalline solid, mp 181–82°C (hexane–$CHCl_3$ 3:1); λ_{max} ($CHCl_3$): 304.2, 282.6, 246.2 nm; ν_{max} (KBr): 1660, 1623, 1596, 1573, 1522, 1503, 1456, 1387, 1365, 1324, 1292, 1231, 1181, 1168, 1142 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.89 (s, 1H, C12–H), 8.32 (d, 1H, *J*=2.20 Hz, C1–H), 7.81–7.59 (m, 2H, arom-Hs), 7.50 (d, 1H, *J*=8.85 Hz, arom-H), 7.38–6.71 (m, 3H, arom-Hs); mass *m/z*: 299 (M^++2, 8), 297 (M^+, 51), 273 (32), 169 (100). Anal. calcd for $C_{16}H_8NO_3Cl$: C, 64.55; H, 2.71; N, 4.71%; found: C, 64.71; H, 2.94; N, 4.99.

3.1.4. 2-Chloro-[1]benzopyrano[2,3-*b*][1,5]-benzothiazepin-13-one (5e). A solution of 6-chloro-2-(*N*-methylanilino)-3-formylchromone (**3b**, 313 mg, 1 mmol) and *o*-aminothiophenol (125 mg, 1 mmol) in xylene (50 mL) was refluxed for 13 h and the solvent was evaporated under vacuum. The crude product was directly crystallized from acetonitrile (20 mL) to afford (**5a**, 298 mg, 0.95 mmol, 95%) as a light yellow crystalline solid, mp 291–92°C (acetonitrile); λ_{max} (MeOH): 326, 279, 247.5, 226 nm; ν_{max} (KBr): 1647, 1621, 1571, 1517, 1482, 1460, 1408, 1320, 1288, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.31 (s, 1H, C12–H), 8.37 (d, 1H, *J*=2.51 Hz, C1–H), 8.06–8.02 (m, 2H, arom-Hs), 7.81–7.55 (m, 4H, arom-Hs); mass *m/z*: 315 (M^++2, 29), 314 (M^++1, 8), 313 (M^+, 60), 169 (92), 111 (49), 71 (100). Anal. calcd for $C_{16}H_8NO_2SCl$: C, 61.25; H, 2.57; N, 4.46%; found: C, 60.96; H, 2.69; N, 4.55.

3.1.5. Reaction of 2-(*N*-methylanilino)-3-formylchromone (3a) with phenylhydrazine. Phenylhydrazine (108 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of **3a** (279 mg, 1 mmol) in refluxing dry-acetonitrile (50 mL) and the contents were refluxed until the reaction completed (9 h, tlc). The solvent was then evaporated under vacuum to 1/5 of its original volume and the solution was kept in a refrigerator. The crystals appeared in 2 h were filtered and washed with cold acetonitrile (1 mL) to obtain a crystalline solid, which was recrystallized from acetonitrile to obtain light yellow crystals (250 mg, 95%), which melted at 218–219°C, but were revealed to be a mixture (7:1, ^{1}H NMR) of two closely related compounds characterized as **6b** and **6b′**; λ_{max} ($CHCl_3$): 327, 331, 297.4, 247.6, 293.6, 261, 244 nm; ν_{max} (KBr): 1689, 1639, 1632, 1614, 1600, 1575, 1558, 1506, 1478, 1438, 1412, 1255, 1190, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.58 (s, 1H, C3–H in **6b**), 8.36 (dd, 1H, *J*=8.04, 1.24 Hz, C5–H in **6b′**), 8.29 (dd, 1H, *J*=8.04, 1.24 Hz, C5–H in **6b**), 8.25 (s, 1H, C3–H in **6b′**), 7.90 (d, 2H, *J*=7.92 Hz, arom-Hs), 7.79–7.67 (m, 2H, arom-Hs), 7.66–7.25 (m, 4H, arom-Hs); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.56 (C4 in **6b**), 172.60 (C4 in **6b′**), 162.06 (C9a in **6b**), 155.63 (C8a in **6b**), 154.37 (C9a in **6b′**), 152.70 (C8a in **6b′**), 138.96 (q), 137.00 (q), 136.74 (C3 in **6b**), 134.49 (C7 in **6b**), 133.95 (CH), 129.69 (CH), 129.43 (CH), 128.12 (CH), 127.71 (CH), 127.07 (CH), 126.82 (CH), 125.32 (CH), 125.15 (CH), 124.04 (C3 in **6b′**), 122.99 (C4a in **6b′**), 122.27 (C4a in **6b**), 121.36 (CH), 119.61 (CH), 118.08 (C8 in **6b**), 117.63 (C8 in **6b′**), 106.73 (C3a in **6b′**), 106.53 (C3a in **6b**); mass *m/z*: 263 (M^++1, 18), 262 (M^+, 100). Anal. calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68%; found: C, 73.43; H, 3.72; N, 10.57.

3.1.6. 6-Chloro-1-phenyl-[1]-benzopyrano[2,3-*c*]pyrazole-4-one (6c). Reaction of 6-chloro-2-(*N*-methylanilino)-3-formylchromone (**3b**, 313 mg, 1 mmol) with phenylhydrazine (108 mg, 1 mmol) according to the procedure described above, afforded **6c** (267 mg, 0.90 mmol, 90%) as a light yellow crystalline solid, mp 281–82°C (acetonitrile); λ_{max} (MeOH): 344, 297.5, 245 nm; ν_{max} (KBr): 1641, 1576, 1558, 1535, 1452, 1420, 1410, 1255, 1188, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.59 (s, 1H, C3–H), 8.29 (bs, 1H, C5–H), 7.80 (bd, 2H, *J*=7.65 Hz, arom-Hs), 7.68–7.43 (m, 5H, arom-Hs); mass *m/z*: 298 (M^++2, 19), 297 (M^++1, 10), 296 (M^+, 49), 169 (80), 111 (47), 83 (49), 71 (100). Anal. calcd for $C_{16}H_9N_2O_2Cl$: C, 64.77; H, 3.06; N, 9.44%; found: C, 64.99; H, 2.92; N, 9.12.

3.1.7. 2-Methoxycarbonylmethylamino-3-formylchromone (7). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was dissolved in refluxing aqueous-acetonitrile (80:20) and a solution of methyl glycinate-hydrochloride (126 mg, 1 mmol) in water (4 mL) and a few drops of triethylamine were added to the above solution. The contents were refluxed for 3 h. The solvent was distilled off and the traces were evaporated under vacuum. The crude product was directly crystallized from methanol to afford **7** (238 mg, 0.91 mmol, 91%) as a cream-colored solid; mp 192–193°C (decomposes); λ_{max} ($CHCl_3$): 270.2, 243 nm; ν_{max} (KBr): 3400 (b), 2897, 1724, 1686, 1616, 1578, 1504, 1481, 1472, 1438, 1406, 1394, 1331 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.97 (bs, 1H, NH), 10.27 (s, 1H, CHO), 8.24 (bd, 1H, *J*=7.53 Hz, C5–H), 7.62 (distorted t, 1H, *J*=7.51 Hz, C7–H), 7.48–7.27 (m, 2H, arom-Hs), 4.37 (d, 2H, *J*=5.80 Hz, N–CH_2), 3.87 (s, 3H, OMe); mass *m/z*: 262 (M^++1, 44), 261 (M^+, 91), 260 (45), 171 (84), 71 (100). Anal. calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36%; found: C, 60.00; H, 4.23; N, 5.52.

3.1.8. 2-Methoxycarbonyl[1]benzopyrano[2,3-*b*]pyrrole-4-one (8). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was dissolved in refluxing aqueous-acetonitrile (80:20, 50 mL) and a solution of methyl glycinate-hydrochloride in water (5 mL) was added to the above solution, followed by potassium carbonate (276 mg, 2 mmol), and the contents were refluxed with stirring for 2 h when a cream-colored crystalline compound separated out, which was filtered, and washed with acetonitrile. (Yield 228 mg, 0.94 mmol, 94%); mp 271–72°C decomposes (water); λ_{max} (MeOH): 262.5, 291 nm; ν_{max} (KBr): 3040

(b), 1715, 1656, 1631, 1582, 1511, 1485, 1420 cm^{-1}; ^1H NMR (200 MHz, D_2O): δ 9.56 (s, 1H, C3–H), 7.62 (bd, 1H, J=7.51 Hz, C5–H), 7.42 (dist. t, 1H, J=7.52 Hz, C7–H), 7.17–7.04 (m, 2H, arom-Hs), 3.75 (s, 3H, OMe); mass *m/z*: 243 (M^+, 11), 242 (M^+-1, 13), 241 (45), 227 (21), 207 (23), 171 (92), 71 (100). Anal. calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76%; found: C, 63.99; H, 3.97; N, 5.92.

3.2. Conversion of 2-methoxycarbonylmethylamino-3-formylchromone (7) to 2-methoxy-carbonyl[1]benzopyrano[2,3-*b*]pyrrole-4-one (8)

2-Methoxycarbonylmethylamino-3-formylchromone (**7**, 131 mg, 0.5 mmol) was dissolved in aqueous-acetonitrile (80:20) and anhydrous potassium-carbonate (100 mg) was added to it. The contents were refluxed with stirring for 3 h, when cream colored crystals of 2-methoxycarbonyl[1]benzopyrano[2,3-*b*]pyrrole-4-one (**8**) separated were filtered and washed with acetonitrile (yield 115 mg, 0.47 mmol, 95%).

3.2.1. *N,N′*-Bis(4-oxo-3-formyl-4H[1]benzopyran-2-yl)-*m*-xylenediamine (9). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was dissolved in refluxing aqueous-acetonitrile (80:20, 50 mL) and a solution of *m*-xylenediamine (68 mg, 0.5 mmol) in acetonitrile (4 mL) was added to it. The contents were refluxed for 3 h and the solvent was distilled off under vacuum. The obtained product was directly crystallized from methanol to obtain the title compound as a white crystalline solid (226 mg, 0.47 mmol, 94%), mp 266–267°C (methanol); λ_{max} ($CHCl_3$): 357.2, 305.4, 298.4, 272.2, 245.2 nm; ν_{max} (KBr): 3210 (b), 1682, 1674, 1632, 1585, 1494, 1468, 1440, 1376, 1358, 1324, 1228 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 11.00 (bs, 2H, NH×2), 10.23 (s, 2H, 2×CHO), 8.22 (bd, 2H, J=7.88 Hz, C5–H×2), 7.60 (unresolved t, 2H, $J\sim$7.12 Hz, C7–H×2), 7.43–7.26 (m, 8H, arom-Hs), 4.78 (d, 4H, J=5.96 Hz, benzylic-Hs); mass (FAB) *m/z*: 482.3 [$(M+H)^+$+1, 40], 481.3 [$(M+H)^+$, 100], 291.3 (8), 279.1 (8). Anal. calcd for $C_{28}H_{20}N_2O_6$: C, 69.99; H, 4.20; N, 5.83%; found: C, 69.60; H, 4.46; N, 5.59.

3.2.2. Reaction of *N,N′*-bis(4-oxo-3-formyl-4*H*[1]benzopyran-2-yl)-*m*-xylenediamine (10) with *m*-xylenediamine. *N,N′*-Bis(4-oxo-3-formyl-4*H*[1]benzopyran-2-yl)-*m*-xylenediamine (**9**, 120 mg, 0.25 mmol) was dissolved in a mixture of acetonitrile-dichloromethane (2:1, 50 mL) and a solution of *m*-xylenediamine (34 mg, 0.25 mmol) in acetonitrile (5 mL) was added to the above stirred solution. The contents were stirred overnight at room temperature. A white solid (**10**), which separated out was filtered and was found to be practically insoluble in any solvent. Yield 139 mg, 0.24 mmol, 96%, mp 251–52°C; ν_{max} (KBr): 3320 (b), 1645, 1590, 1539, 1469, 1452, 1422, 1340, 1247, 1232, 1195, 1128, 1105, 1087 cm^{-1}; mass (FAB) *m/z*: 583.3 [$(M+H)^+$+2, 9], 582.3 [$(M+H)^+$+1, 41], 581.3 [$(M+H)^+$, 100], 291.3 (6). Anal. calcd for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65%; found: C, 74.12; H, 4.81; N, 9.77.

3.2.3. Reaction of 3a with *m*-aminophenol leading to macrocycle (11). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was dissolved in xylene (50 mL) and a solution of *m*-aminophenol (109 mg, 1 mmol) in xylene (10 mL) was added to the above solution. The contents were refluxed with stirring and the progress of the reaction was monitored with tlc. After 20 h the solvent was evaporated to 1/4 of its original volume when a dark brown crystalline solid (**11**) separated out, which was filtered and washed with a little cold xylene and recrystallized from acetone. Yield 248 mg, 0.313 mmol, 94%, mp >275°C (acetone); λ_{max} ($CHCl_3$): 348.6, 268.6, 245 nm; ν_{max} (KBr): 1671, 1616, 1538, 1492, 1428, 1387, 1374, 1313, 1276, 1241, 1230, 1164 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6–$CDCl_3$, 1:1): δ 9.16 (s, 3H, HC=N×3), 8.22 (bd, 3H, J=7.85 Hz, C5–H×3), 8.10–8.06 (m, 6H, arom-Hs), 7.86–7.82 (m, 3H, arom-Hs), 7.64–7.60 (m, 3H, arom-Hs), 7.50–7.42 (m, 6H, arom-Hs), 7.26–7.21 (m, 3H, arom-Hs); ^{13}C NMR (50 MHz, DMSO-d_6–$CDCl_3$, 1:1): δ 176.54 (C=O), 162.40 (C=N), 157.08 (C2), 154.93 (C8a), 150.65 (q), 138.29 (q), 135.24 (CH), 131.06 (CH), 125.66 (CH), 123.65 (CH), 120.16 (CH), 120.10 (C4a), 119.30 (C8), 117.48 (CH), 112.57 (C3), 107.92 (CH); mass (FAB) *m/z*: 792.4 [$(M+H]^+$+2, 21], 790.3 [$(M+H]^+$, 76], 624.6 (100). Anal. calcd for $C_{48}H_{27}N_3O_9$: C, 73.00; H, 3.45; N, 5.32%; found: C, 73.39; H, 3.79; N, 5.20.

3.2.4. 1,1′-Bis(4-oxo-3-formyl-4*H*[1]benzopyran-2-yl)-4,4′-bipiperidine (12). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was dissolved in dry-acetonitrile (200 mL) and to the stirred solution were added anhydrous potassium carbonate (276 mg, 2 mmol), and 4,4′-bipiperidine-dihydrochloride (121 mg, 0.5 mmol). The contents were stirred at 80°C until the completion of reaction (6 h, tlc). The solvent was distilled off and the solid mass was dissolved in chloroform (200 mL), filtered and the solvent was distilled off to afford the title compound as a white crystalline solid (233 mg, 0.455 mmol, 91%), mp 273–274°C (chloroform–hexane 1:3); λ_{max} ($CHCl_3$): 321, 283.6, 243.4 nm; ν_{max} (KBr): 1673, 1618, 1546, 1462, 1424, 1413, 1338 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 10.14 (s, 2H, 2×CHO), 8.18 (bd, 2H, J=7.82 Hz, 2×C5–H), 7.61 (dist. t, 2H, J=7.22 Hz, 2×C7–H), 7.41–7.26 (m, 4H, arom-Hs), 4.10 (d, 4H, J=12.74 Hz, C2′-Hs-*axial*), 3.24 (unresolved t, 4H, C2′-Hs-*equitorial*), 2.00–1.93 (m, 4H, C3′-Hs-*axial*), 1.60–1.54 (m, 4H, C3′-Hs-*equatorial*), 1.24–1.20 (m, 2H, C4–H and C4′–H); mass (FAB) *m/z*: 514.3 [$(M+H)^+$+1, 40], 513.3 [$(M+H)^+$, 100], 485.3 (8), 360.4 (13), 341.3 (14), 338.5 (11). Anal. calcd for $C_{30}H_{28}N_2O_6$: C, 70.30; H, 5.51; N, 5.47%; found: C, 70.09; H, 5.23; N, 5.62.

3.3. General procedure for the reaction of 3a,b with 1,3-diaminobenzene in aqueous-acetonitrile

Compounds (**3a**,**b**, 1 mmol) were dissolved in refluxing aqueous-acetonitrile (50 mL) and solutions of *m*-phenylenediamine (108 mg, 1 mmol) in acetonitrile (10 mL) were added to the above solutions. The contents were refluxed with stirring for 6 h after which the solvent was evaporated and the crude was purified over silica gel column (60–120 mesh) using hexane–ethyl acetate (9:1) as eluent. The products (**13a**,**b**) were recrystallized from acetonitrile.

3.3.1. 8-Amino-quinolino[2,3-*b*]chroman-12-one (13a). 2-(*N*-Methylanilino)-3-formylchromone (**3a**, 279 mg, 1 mmol) was treated with *m*-phenylene-diamine (108 mg,

1 mmol) to afford the title compound (**13a**, 176 mg, 0.67 mmol, 67%) as a dark brown solid, mp 267–68°C (acetonitrile); ν_{max} (KBr): 3350 (b), 3134 (b), 1622 (w), 1614 (w), 1577, 1552, 1535, 1467, 1432, 1347, 1331, 1290, 1262, 1189, 1120, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.05 (s, 1H, C11–H), 8.27 (dd, 1H, J=7.81, 2.60 Hz, C1–H), 7.85 (d, 1H, J=8.80 Hz, C10–H), 7.68 (split t, 1H, J~7.65, 2.60 Hz, C3–H), 7.54 (dd, 1H, J=7.60, 2.31 Hz, C4–H), 7.32 (m, 1H, C2–H), 7.09 (bs, 1H, C7–H), 7.00 (dd, 1H, J=8.80, 2.32 Hz, C9–H), 4.52 (bs, 2H, exchangeable with D_2O, NH_2); mass m/z: 263 (M^++1, 21), 262 (M^+, 81), 171 (76), 121 (82), 71 (100). Anal. calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68%; found: C, 73.02; H, 3.97; N, 10.97.

3.3.2. 2-Chloro-8-amino-quinolino[2,3-*b*]chroman-12-one (13b). 6-Chloro-2-(*N*-methylanilino)-3-formylchromone (**3b**, 313 mg, 1 mmol) was treated with *m*-phenylenediamine (108 mg, 1 mmol) to obtain the title compound (**13b**, 214 mg, 0.72 mmol, 72%) as a dark brown solid, mp 274–275°C (acetonitrile); λ_{max} (MeOH): 418.5, 241.5, 225 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H, C11–H), 8.26 (d, 1H, J=2.59 Hz, C1–H), 7.84 (d, 1H, J=8.84 Hz, C10–H), 7.67 (dd, 1H, J=7.60, 2.59 Hz, C3–H), 7.54 (d, 1H, J=7.6 Hz, C4–H), 7.08 (bs, 1H, C7–H), 6.99 (dd, 1H, J=8.84, 2.32 Hz, C9–H), 4.51 (bs, 2H, exchangeable with D_2O, NH_2); mass m/z: 298 (M^++1, 13), 297 (M^+, 10), 296 (M^+−1, 45), 171 (84), 71 (100). Anal. calcd for $C_{16}H_9N_2O_2Cl$: C, 64.77; H, 3.06; N, 9.44%; found: C, 64.49; H, 3.31; N, 9.97.

3.4. General procedure for the preparation of tetradentate ligands

To solutions of compound (**2a**, 1 mmol) in refluxing dry-acetonitrile (50 mL) were added solutions of corresponding diamines (1 mmol) in acetonitrile (10 mL), after which the contents were cooled and stirred at room temperature for 12 h. Yellow colored crystalline solids separated out, were filtered and the second crop was recovered by concentrating the filtrates to 1/5 of their original volume and cooling.

3.4.1. Reaction of 2a with *m*-xylenediamine leading to ligand 14a. Compound (**2a**, 265 mg, 1 mmol) was reacted with *m*-xylenediamine (136 mg, 1 mmol) to afford the title compound as a crystalline yellow solid (306 mg, 0.485 mmol, 97%), mp 284–285°C (acetonitrile); ν_{max} (KBr): 3050 (b), 2940 (b), 1665 (s), 1627 (s), 1611 (s), 1580 (s), 1481, 1448, 1341, 1213 cm^{-1}; λ_{max} ($CHCl_3$): 368, 301.5, 287.5, 246.5 nm; ^1H NMR (200 MHz, $CDCl_3$): δ 12.34 (bs, 2H, N–H), 8.70 (bs, 2H, 2×HC═N), 8.14 (d, 1H, J=7.50 Hz, C5–H), 7.57–7.07 (m, 20H, arom-Hs), 4.79 (bs, 4H, benzylic Hs); ^{13}C NMR (50 MHz, $CDCl_3$): 177.27 (C═O), 156.75 (C═N), 154.58 (C2), 154.03 (C8a), 144.06 (q), 137.41 (CH), 133.82 (CH), 129.85 (CH), 128.66 (CH), 127.11 (CH), 126.26 (CH), 123.74 (CH), 123.28 (CH), 121.02 (C4a), 116.54 (C8), 97.28 (C3), 54.76 (CH_2). Anal. calcd for $C_{40}H_{30}N_4O_4$: C, 76.17; H, 4.79; N, 8.88%; found: C, 76.41; H, 5.07; N, 8.64.

3.4.2. Reaction of 2a with ethylenediamine leading to ligand 14b. Compound (**2a**, 265 mg, 1 mmol) was treated with ethylenediamine (60 mg, 1 mmol) to afford the title compound as a crystalline yellow solid (266 mg, 0.48 mmol, 96%), mp 211–212°C (acetonitrile); ν_{max} (KBr): 3100 (b), 2980 (b), 1650 (s), 1605 (s), 1581 (s), 1487, 1444, 1393, 1346, 1290, 1251, 1213 cm^{-1}; λ_{max} ($CHCl_3$): 368, 319.5, 286.5, 246.5 nm; ^1H NMR (200 MHz, $CDCl_3$): δ 12.40 (bs, 2H, N–Hs), 8.64 (s, 2H, HC═N), 8.14 (d, 2H, J=7.52 Hz, C5–Hs), 7.47 (dis. t, 2H, J=7.24 Hz, C7–Hs), 7.24–6.91 (m, 14H, arom-Hs), 3.69 (s, 4H, $-CH_2-$×2); ^{13}C NMR (50 MHz, $CDCl_3$): 176.31 (C═O), 157.68 (C═N), 153.51 (C2), 152.1 (C8a), 141.2 (q), 133.55 (CH), 128.55 (CH), 126.19 (CH), 123.99 (CH), 122.99 (CH), 121.31 (C4a), 116.54 (C8), 96.94 (C3), 53.61 (CH_2). Anal. calcd for $C_{34}H_{26}N_4O_4$: C, 75.63; H, 4.73; N, 10.10%; found: C, 75.49; H, 4.41; N, 9.81.

3.4.3. Reaction of 2a with *m*-phenylenediamine leading to ligand 14c. Compound (**2a**, 265 mg, 1 mmol) was treated with *m*-phenylenediamines (108 mg, 1 mmol) to afford the title compound as a crystalline brownish solid (283 mg, 0.47 mmol, 94%), mp 244–46°C decomposes (acetonitrile); ν_{max} (KBr): 3060 (b), 1662 (Sh), 1621 (Sh), 1567, 1476, 1448, 1302 cm^{-1}; λ_{max} ($CHCl_3$): 397, 248.5, 319, 290.5 nm; ^1H NMR (200 MHz, $CDCl_3$): δ 13.84 (bs, 2H, N–H), 9.10 (bs, 2H, HC═N), 8.14 (d, 2H, J=7.90 Hz, C5–H), 7.55–7.10 (m, 20H, arom-Hs). Anal. calcd for $C_{38}H_{26}N_4O_4$: C, 75.73; H, 4.35; N, 9.30%; found: C, 75.59; H, 4.13; N, 9.77.

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