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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of tetracyclic aza-/oxa-naphthalen-8-ones and their antimicrobial activity

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Abstract Tetracyclic azanaphthalen-8-ones are synthesized by condensing 3-bromo-4-methyl benzo[h]-chromen-2-one with different primary aromatic amines. 3-Bromo-4-methylbenzo[h]chromen-2-one is synthesized by bromination of 4-methylbenzo[h]chromen-2-one using *N*-bromosuccinimide. Condensation of 3-bromo-4-methylbenzo[h]chromen-2-one with different secondary cyclic amines gave tetracyclic oxanaphthalen-9-one. All the synthesized compounds were screened for their antimicrobial activity and they show good results.

Keywords α-Naphthol · Azanaphthalen-8-ones · Oxanaphthalen-8-one · Biological activity

Introduction

Naphthopyrones are reported to possess various biological activities (Braccio *et al.*, 2003; Braccio *et al.*, 1995; Roma *et al.*, 1998). Several furonaphthopyrones are reported to possess DNA-intercalating properties (Fu *et al.*, 1999a; Xuhong *et al.*, 1996 Fu et *al.*, 1996). Furo- and thionaphthopyrones have been reported as potential mono functional photo biological agents (Fu and Xuhong, 1998; Fu and Xuhong, 1996; Fu *et al.*, 1999b) to DNA. Pannorin, a derivative of naphthopyrone, a new coenzyme A reductase inhibitor produced by chrysosporium pannorum (Haruo *et al.*, 1991), is the rate limiting enzyme in cholesterol synthesis. Considering the above results and in continuation of our work on benzo pyrone derivatives (Soman, 2004; Patel and Soman, 2010; Soman and Thaker, 2009), this report extends investigation on the synthesis of tetracyclic aza/oxa-naphthalen-8-ones and detailing biological activity of the synthesized compounds.

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Results and discussion

Pechmann condensation (Robertson *et al.*, 1931) of α-naphthol with ethylacetoacetate gave 4-methyl-benzo[h]chromen-2-one **1**. Bromination of **1** with *N*-bromosuccinimide in the presence of benzoyl peroxide and light (100 W bulb) in refluxing chloroform was expected to give 4-bromomethylbenzo[h]chromen-2-one, instead gave 3-bromo-4-methylbenzo[h]chromen-2-one **2**. The structure of **2** was confirmed by IR, ^{1}H-NMR and mass spectra. In ^{1}H-NMR of **1**, the presence of a sharp singlet at δ 6.35 integrated for one proton clearly indicated C-3 proton, singlet at δ 2.50 integrated for three protons indicated methyl group at C-4. After bromination in the ^{1}H-NMR of **2**, sharp singlet integrated for one proton at δ 6.35 was disappeared and methyl signal for three protons at δ 2.71 was clearly observed. All other aromatic protons were observed in the range of δ 7.62–8.56. This indicated bromination with *N*-bromosuccinimide has occurred at third position of chromen-2-one. Moreover, mass spectrum of **2** also supported with M+2: M+ (1:1) signal at 291 and 289. Reference [15–18] (Bacovescu, 1910; Dey and Lakshminarayanan, 1934; Carnduff and Marks, 1977; Carnduff and Marks, 1975)-reported bromination of 1-Methylbenzo[f]chromen-3-one with bromine in acetic acid gave 3-bromo-1-methylbenzo[f]chromen-3-one.

We had condensed **2** with different primary aromatic amines expecting to get 4-aminomethyl derivatives of benzo-[h]-chromen-2-ones, as we had prepared furopsoralenamines

(Patel and Soman, 2010). But, to our surprise, the product obtained was tetracyclic (**3 a–d**). Carnduff (Carnduff and Marks, 1977; Carnduff and Marks, 1975) observed that alkaline hydrolysis of 2-Bromo-1-methylbenzo[f]chromen-3-one gave two unusual products involving skeletal rearrangement. **2** on condensation with *p*-toluidine gave 9-*p*-Tolyl-6b,7,9,9a-tetrahydro-10-oxa-9-aza-pentaleno[2,1-a]naphthalene-8-one (**3a**). The structure of this compound was confirmed by IR and ^{1}H-NMR analyses Scheme 1 (Soman and Thaker, 2010).

In ^{1}H-NMR, a singlet for three protons at δ 2.39 indicated $-CH_3$, two double doublets integrated for one proton each at δ 2.82–2.88 with $J = 2.4$ Hz and δ 3.15–3.24 with $J = 3.4$, 9.6 Hz clearly indicated $-CH_2$ proton, while the multiplet at δ 4.34–4.39 for one proton indicated proton at ring junction. The doublet for one proton at δ 6.60–6.63 indicated another proton at ring junction, sandwiched between O and N. Signals from δ 7.26–7.96 indicated other aromatic protons. The IR spectrum showed carbonyl band at 1,709 cm^{-1}, which indicated cyclic five-membered amide.

Formation of similar product was confirmed by single crystal analysis of 8-*p*-Tolyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno[1,2-a]naphthalen-9-one which was formed upon condensation of *p*-toluidine with 2-bromo-1-methylbenzo[f]chromen-3-one (Soman and Thaker, 2010), the CCDC no. of which is 766458.

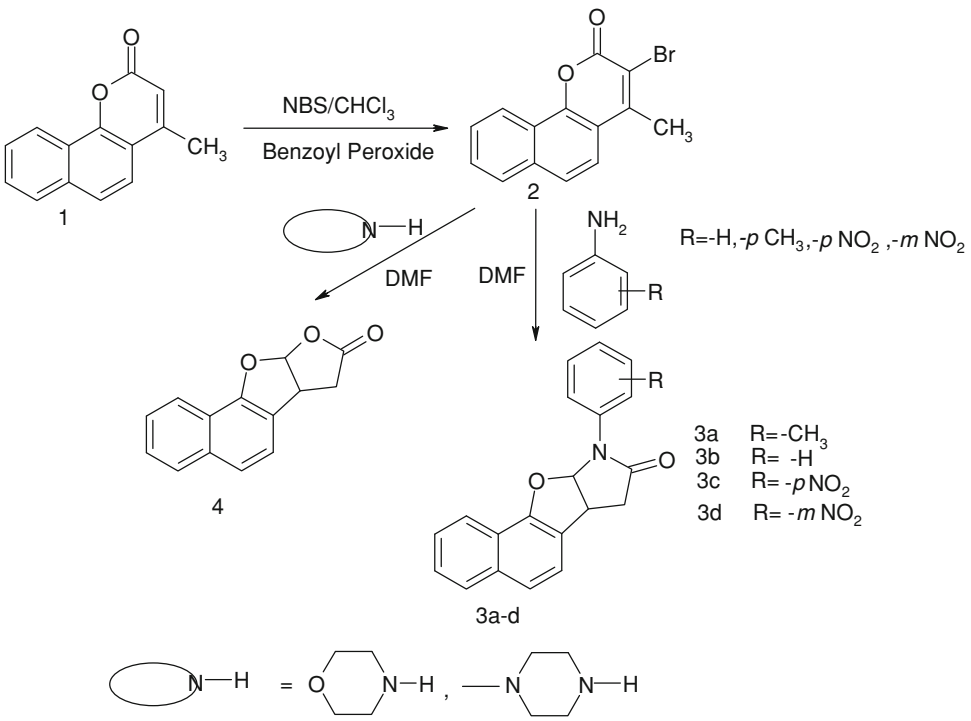
Similar compounds **3 a–d** were obtained when different primary aromatic amines were condensed like aniline, p-toluidine, m-nitro aniline and p-nitro aniline with **2**.

The formation of **3 a–d** was further supported by the fact that when this reaction was carried out in solvent like absolute ethanol, the starting material 3-Bromo-4-methylbenzo[h]chromen-2-one was recovered. When dimethylformamide (DMF) was used as solvent reaction gave the product.

When we have condensed different cyclic secondary amines like morpholine and N-methyl piperazine with **2**, it gave the only product **4** which was showing same ^{1}H-NMR pattern as **3 a–d**. Its IR spectrum showed carbonyl stretching frequency at 1,770 cm^{-1}. Moreover, Lassaigne's test and elemental analysis of product **4** indicated the absence of nitrogen. Since nitrogen is absent in the sample, it indicated the five-membered lactone ring which is supported by IR stretching frequency at 1,770 cm^{-1}. Thus, the formation of 6b,9a-Dihydro-7H-9,10-dioxa-pentaleno[2,1-a]naphthalene-8-one **4** was confirmed. Further formation of this product was supported by single crystal analysis of 10, 10a-Dihydro-7aH-7,8-dioxa-pentaleno[1,2-a]naphthalen-9-one, which was formed when we have condensed morpholine with 2-bromo-1-methylbenzo[f]chromen-3-one (Soman and Thaker, 2010), the CCDC no. of which is 766459.

The formation of cyclic lactone **4** indicated that water must be attacking and the secondary amine is eliminated during reaction. Thus, we have observed the formation of tetracyclic ring during the condensation of 3-bromo-4-methyl benzo[h]chromen-2-one with primary aromatic amines as well as secondary cyclic amines. Mashelkar

Scheme 1



et al. (2001)) reported the formation of tetracyclic product by oxidation of benzocoumarin-4-acetic acid with selenium dioxide and further reactions.

It was thought that these novel products obtained in the case of β-naphthol (Soman and Thaker, 2010) may be due to the steric hinderance of naphthalene ring, which may not be observed in the case of α-naphthol because the lactone ring at the 3rd position is not sterically hindered. But similar results were obtained (Soman and Thaker, 2010) which was supported by IR and ^{1}H-NMR of products.

Experimental

The melting points were determined in scientific open capillaries and are uncorrected. The IR spectra were determined as KBr pellets on a Schimadzu model IR-408 spectrophotometer. The ^{1}H-NMR and ^{13}C NMR spectra were recorded using Bruker DRX 400 MHz in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra were recorded on a GC–MS spectrometer. Elemental analyses were performed on Carlo Erba-1108 elemental analyser. Acme's Silica gel (mesh size 60–120) was used for column chromatography.

4-Methylbenzo[h]chromen-2-one **1**

In the mixture of α-naphthol (10 gm, 0.0,694 mol) and ethylacetoacetate (9.0 ml, 0.0,694 mol), H_2SO_4 (20 ml) was added slowly with constant stirring and allowed to keep overnight. It was poured into crushed ice with constant stirring. The crude product filtered and recrystallized from ethanol as yellow crystals. Yield 53 %, mp ref. [14] 165–167 °C. IR (KBr): ν_{max}, cm^{-1}: 3071, 2923, 2854, 1716, 1610, 1504, 1377. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.50 (s, 3H, CH_3), 6.35 (s, 1H, C3-H), 7.58–7.87 (m, 5H, C5, C6, C7, C8, C9-H), 8.51–8.56 (m, 1H, C10-H). Anal. Calcd. for $C_{14}H_{10}O_2$ (210): C, 80.00; H, 4.76. Found: C, 80.11; H, 4.59.

3-Bromo-4-methylbenzo[h]chromen-2-one **2**

To a solution of **1** (2 gm, 0.0095 mol) dissolved in 25 ml chloroform, *N*-bromosuccinimide (1.7 gm, 0.0095 mol) and a 10 mg benzoyl peroxide (catalytic amount as an initiator) were added and refluxed in a photoreactor for 10 h. using 100-W bulb. It was filtered, the excess solvent distilled off, crude product filtered and washed with methanol and recrystallized from toluene. Yield 73 %, mp 192–193 °C. IR (KBr): ν_{max}, cm^{-1}: 3160, 3072, 1714, 1635, 1610, 1375, 1294, 1193, 851, 810. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.71 (s, 3H, $-CH_3$), 7.62–7.73 (m, 4H, C6, C7, C8, C9-H), 7.86–7.88 (m, 1H, C5-H), 8.54–8.56 (m, 1H, C10-H). Mass: M+2: M+ (1:1) 291, 289(b), 245, 260, 211(M-Br), 181, 152. Anal. Calcd. for $C_{14}H_9O_2Br$ (288.5): C, 58.23; H, 3.11. Found: C, 58.12; H, 3.30.

General procedure for the preparation of aza naphthalen-8-ones (**3a–d**)

A mixture of **2** (0.01 mol), different primary aromatic amines (0.021 mol) and DMF (20 ml) was refluxed for 6 h. The reaction mixture was cooled, poured into crushed ice and filtered. The crude product was purified by column chromatography using petroleum ether: ethyl acetate (9:1) as eluent.

*9-p-Tolyl-6b,7,9,9a-tetrahydro-10-oxa-9-aza-pentaleno[2,1-a]naphthalen-8-one (**3a**)*

Yield 21 %, mp 132-133 °C. IR (KBr): ν_{max}, cm^{-1}: 3055, 2920, 1716, 1613, 1514, 1469, 1443, 1382, 1263. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H, CH_3), 2.82–2.88 (dd, 1H, J_1 = 2.4 Hz, H at $-CH_2$), 3.15–3.24 (dd,1H, J = 9.6 Hz, H at $-CH_2$), 4.34–4.39 (m, 1H, J = 7.5 Hz, H at ring junction), 6.60–6.63 (d, 1H, J = 7.2 Hz, H at ring junction), 7.26–7.28 (d, 1H, J = 5.74 Hz, C2,C5-H), 7.34–7.37 (d, 1H, J = 8.4 Hz, C4-H), 7.46–7.55 (m, 5H, C1, C3, C6, C3′, C5′-H), 7.83–7.86 (m, 1H, C2′-H), 7.93–7.96 (m, 1H, C6′-H) Anal. Calcd. for: $C_{21}H_{17}NO_2$ (315): C, 80.00; H, 5.39; N, 4.44. Found: C, 79.91; H, 5.51; N, 4.30.

*9-p-Phenyl-6b,7,9,9a-tetrahydro-10-oxa-9-aza-pentaleno[2,1-a]naphthalen-8-one (**3b**)*

Yield 39 %. mp 208–210 °C. Anal. Calcd. for: $C_{20}H_{15}NO_2$ (301): C, 79.73; H, 4.98; N, 4.65. Found: C, 79.53; H, 4.79; N, 4.77.

*9-p-Nitrophenyl-6b,7,9,9a-tetrahydro-10-oxa-9-aza-pentaleno[2,1-a]naphthalen-8-one (**3c**)*

Yield 30 %, mp 237–239 °C. IR (KBr): ν_{max}, cm^{-1}: 3066, 1719, 1635, 1598, 1516, 1472, 1377, 1344, 1136, 1088. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.99–3.05 (dd, 1H, J = 3.8 Hz, H at $-CH_2$), 3.34–3.41 (dd, 1H, J = 10.1 Hz, H at $-CH_2$), 4.56–4.62 (m, 1H, J_1 = 3.7, J_2 = 7.1 Hz, H at ring junction), 6.77–6.79 (d, 1H, J = 7.9 Hz, H at ring junction), 7.13–7.15 (d, 1H, J = 8.8 Hz, C5-H), 7.39–7.43(m, 1H, C2-H), 7.55–7.62 (m, 2H, J = 8.8 Hz, C3, C4-H), 7.78–7.79 (m, 2H, C1, C6-H), 8.10–8.12 (d, 2H, J = 9.2 Hz, C2′, C6′-H), 8.30–8.32 (d, 2H, J = 9.4 Hz, C3′, C5′-H). Anal. Calcd. for $C_{20}H_{14}N2O_4$ (346): C, 69.36; H, 4.04; N, 8.09. Found: C, 69.16; H, 4.24; N, 8.21.

Table 1 Zone of inhibition in mm (antibacterial activity)

Compound	*Staphylococcus aureus*		*Escherichia coli*		*Micrococcus luteus*	
	mm	MIC	mm	MIC	mm	MIC
3a	11	250	10	300	18	250
3b	10	250	11	300	11	300
3c	08	300	08	300	10	300
3d	21	200	09	400	09	400
4	10	250	11	300	10	300
Ampicillin	05	25	04	25	05	25

*9-m-Nitrophenyl-6b,7,9,9a-tetrahydro-10-oxa-9-aza-pentaleno[2,1-a]naphthalen-8-one (**3d**)*

Yield 49 %, mp 141–143 °C. IR (KBr): ν_{max}, cm^{-1}: 3412, 3070, 2925, 1719, 1630, 1528, 1475, 1378, 1267, 1143, 1085, 811, 738. Anal. Calcd. for: $C_{20}H_{14}N_2O_4$ (346): C, 69.36; H, 4.04; N, 8.09. Found: C, 69.41; H, 4.21; N, 8.11.

General procedure for the preparation of 6b, 9a-Dihydro-7H-9, 10-dioxa-pentaleno[2,1-a]naphthalen-8-one (**4**)

A mixture of **2** (0.01 mol) and different cyclic secondary amines (0.021 mol) were refluxed in DMF (20 ml) for 6 h. The reaction mixture cooled, poured into crushed ice and filtered. The crude product was purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent. Yield 31 %, mp 84 °C. IR (KBr): ν_{max}, cm^{-1}: 3050, 1774(>C=O), 1631, 1578, 1520, 1464. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.96–3.02 (dd, 1H, $J = 2.44$ Hz, H at $-CH_2$), 3.20–3.27 (dd, 1H, $J = 9.84$ Hz, H at $-CH_2$), 4.53–4.58 (m, 1H, H at ring junction), 6.71–6.72 (d, 1H, $J = 6.4$ Hz, H at ring junction), 7.19–7.21 (d, 1H, $J = 8.8$ Hz, C5-H), 7.39–7.44 (m, 1H, C2-H), 7.55–7.56 (d, 2H, C3, C4-H), 7.79–7.82 (d, 1H, $J = 8.9$ Hz, C6-H), 7.87–7.89 (d, 1H, $J = 8.2$ Hz, C1-H). Anal. Calcd. for $C_{14}H_{10}O_3$ (226): C, 74.33; H, 4.42. Found: C, 74.24; H, 4.59.

Biological activity

Aza/Oxa naphthalene-8-ones were screened for their antibacterial and antifungal activity.

Antibacterial activity

All the synthesized compounds were tested for their antibacterial activity against *Escherichia coli* (Gram negative), *Staphylococcus aureus* (Gram positive) and *Micrococcus luteus* (Gram positive) by cup plate method [21] (Barry, 1977) at 100 ppm concentration in DMF solvent. Ampicillin was used as standard drug. All compounds showed excellent activity against all types of Gram positive and Gram negative strains.

Experimental

Antibacterial activity of all the synthesized compounds was tested in vitro by (cup plate method) serial agar dilution in which bacterial strains of *S. aureus* (Gram positive), *E. coli* (Gram negative) and *M. luteus* (Gram positive) were used, using serial agar dilution (cup plate method).

The two microorganisms were cultured in petri dishes containing agar medium, cups (8 mm) were put onto the dishes and each synthesized compound dissolved in DMF (0.1 ml of 10 mg/ml) was added into the cups under aseptic condition. Then, the petri dishes were incubated at 37 °C for 24 h. The zone of inhibition of the growth of the bacteria, which were produced by diffusion of the compounds from the cup into the surrounding medium, was measured to evaluate the antibacterial activity. Each experiment was repeated twice. DMF was used as a positive control for the experiments. Results are shown in Table 1.

Antifungal activity

All the synthesized compounds were tested for their antifungal activity by poison-food method [22] (Nene and Thapliyal, 1979). They were tested against *Fusarium roseum*, *Alternaria sp.* and *Cladosporium* sp. at 100 µg concentration. DMF was used as control. All compounds showed excellent antifungal activity against all fungi which were used in experiment.

Experimental

Antifungal activity of all the synthesized compounds were tested in vitro in which fungal strains of *F. roseum*, *Alternaria* sp. and *Cladosporium* sp. were used using Potato Dextrose Agar (PDA) medium (Poisoned Food Technique). PDA was prepared as per M096 HiMedia laboratories.

The standard fungi *F. roseum*, *Alternaria* sp. and *Cladosporium* sp. culture were grown on PDA slants at room

Table 2 % Inhibition of growth (antifungal activity) zone of inhibition in mm

Compound	*Fuserium roseum*		*Alternaria* species		*Cladosporium* species	
	mm	MIC	mm	MIC	mm	MIC
3a	50	200	60	200	–	–
3b	45	200	57.5	200	–	–
3c	25	250	30	250	55	200
3d	25	250	75	200	–	–
4	45	200	37.5	200	65	200

temperature. Mycelial growth inhibition of *F. roseum*, *Alternaria* sp. and *Cladosporium* sp. were evaluated by the poisoned food technique, where the inhibition in growth of the fungal strain was observed on PDA. The stock solution (100 μg) was made from each of the test compounds using DMF. The required % concentrations of the compounds (mg/ml) were obtained by mixing the appropriate amount of the stock solution with 20 ml of molten PDA. The amended PDA was poured into petridishes and allowed to set.

An inoculums of the fungus obtained from 7 days old axenic culture, grown as above, was placed at the centre of the amended agar medium. Each experiment was performed in triplicate. The diameter of the fungal colony was measured after 4 days and then 7 days at 26 + 1 °C and the % inhibition was calculated by the following equation:

The result has been shown in Table 2.

$$\%\ \text{inhibition} = \frac{\text{growth area in reference} - \text{growth area in sample}}{\text{growth area in reference}} \times 100$$

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