

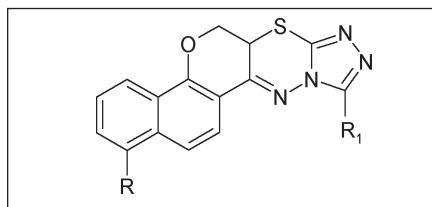
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Chemoselective synthesis of novel hetero cyclopenta[*b*]chrysene derivatives, namely, 6-Aryl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4a-j**) under neutral condition has been described. These molecules exhibited good to excellent anti-bacterial activities.

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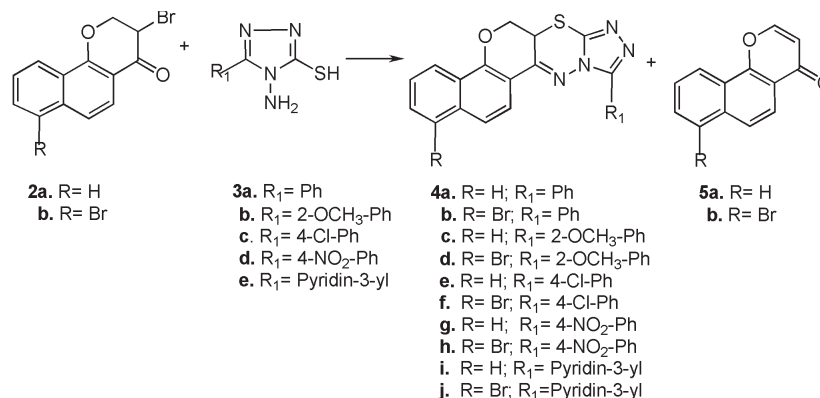
Steroids are widely distributed in nature and its members display much diversity in molecular structure [1a-c]. Heterocyclic derivatives of steroids comprised of molecules with structural features characteristic of steroids such as tetracyclic cyclopenta[*a*]phenanthrene framework, with or without aromatic A and/or B rings as well as heteroatom substitution in the tetracyclic structure. Literature survey revealed that the syntheses of new heterosteroidal molecules has received unabated attention from synthetic chemists. Studies in this field are mainly comprised of finding new pathways [2,3] for the development of heterosteroidal molecules and directed efforts for achieving molecules with substantial bioactivities [1a-c,4-9]. The present paper describes the synthesis of novel D homo hetero equilenin derivatives, namely, 6-aryl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4a-j**).

Pyran [10], 1,3,4-thiadiazine [11a,b], and 1,3,4-triazole [12a,b] are the heterocycles with reported useful bioactivi-

ties and hence these subunits have been incorporated in many new fused heterocycles [11a,b-13a,b]. These factors made us consider the syntheses of a new class of heterosteroids with the presence of pyran, thiadiazine and triazole heterocycles.

Results and Discussion.

It was decided to use 3-bromonaphthopyranones (**2a-b**) as a platform for the synthesis of target molecules **4a-j**. The reaction of α -bromoketone with 4-amino-3-mercapto-5-aryl-1,2,4-triazoles (**3a-e**) to afford *s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives are reported to take place in presence of a base [12a]. But it was soon discovered that in the presence of any base, 3-bromonaphthopyranone (**2a**), gave the major or almost exclusive product as the dehydrohalogenated product, namely, naphtho[1,2-*b*]pyran-4-one (**5a**) [14]. Hence it became necessary to avoid the use of base during the reaction. Accordingly it was decided to



carry out the reactions between **2a,b** with **3a-e** under neutral conditions to keep the formation of **5a** and **5b** to a minimum. Several solvents such as methanol, THF, dioxane, DMSO and DMF were tried for the said reaction between **2a,b** and **3a-e**. In some solvents like methanol the major product was the elimination product **5a/b**, while in solvents like THF and dioxane the reaction was sluggish with substantial formation of **5a/b**. In DMSO the entire reaction mixture became colored and the yield of the desired compound was only about 30%. The most satisfactory results with regard to selective formation of **4a-j** and reaction time were obtained when DMF was employed as a solvent.

The compounds formed were adequately characterized by elemental analysis, mass spectrometry, pmr, cmr and ir spectroscopic techniques. *e.g.*, the mass spectrum of compound **4a** shows ions of m/z 370 (M^+), 371 ($M+1$)⁺ and 372 ($M+2$)⁺ as well as other ions. The pmr spectrum exhibited signals for 11 aromatic protons between δ 7.5 and 8.15 ppm, of which the C-14(H) proton was found to be the most deshielded. The 2 protons on C(2) gave two separate peaks as dd at δ 5.05 and δ 5.35 ppm with J values

5.6 and 10.8 Hz for the signal at δ 5.05 and 5.6 and 12 Hz for the signal at δ 5.35 ppm. These two distinct signals for the 2 protons on C(2) indicated the conformational rigidity of the pyran structure and the equatorial like proton most probably was appearing downfield due to the oxygen electron pair proximity effect. The C(2a) proton appeared at δ 4.6 as a triplet in place of the expected dd. The two different J values of 10.8 and 12 Hz. were however obtained, indicating that the two doublets have merged together to give an enhanced middle peak. The structure was further confirmed by cmr, which exhibited two aliphatic signals for C(2) and C(2a) at δ 67.27 and δ 34.34 respectively. The aromatic carbon resonances were observed at δ 111.31 ppm and onwards. The C(6), C(3a) and C(8a) carbons were found to be deshielded and appeared at δ 156.04, 152.16 and 148.33 ppm respectively. Table 1 presents the percentage formation of **4a-j** and **5a-b**. The modified reaction conditions gave us the desired **4a-j** chemoselectively over the dehydrohalogenated products **5a,b**.

Biological Activity.

The *in-vitro* antibacterial activity of these compounds, **4a-j**, (250 μ g/ml) were tested against gram-positive [*Streptococcus pyogen*, *Bacillus subtilis*] and gram-negative bacteria [*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*] which were clinical isolates from Hafkkins Laboratory, Mumbai (India). They were maintained on nutrient agar (Himedia Lab. Ltd., India) slants at 4 °C prior to use for antimicrobial susceptibility test. The bioassay of these compounds was carried out by agar cup method (Spooner and Skyes, 1972) against test microorganism. All these tests were carried out in triplicate and the average values for zone of inhibition in millimeters (mm) were taken after 24 hr of incubation. The compounds were dissolved in methanol. Ampicillin was used as positive control for both gram-positive gram-negative bacteria's.

Table 1

Showing the result of reaction between **2a,b** and **3a-e** and the chemoselectivity shown.

Compound 4a-j	R1	R2	%Yield 4a-j	5a-b
a	H	H	71	29
b	Br	H	69	31
c	H	2-OCH ₃	72	28
d	Br	2-OCH ₃	61	39
e	H	4- Cl-Ph	62	38
f	Br	4- Cl-Ph	65	35
g	H	4- NO ₂ -Ph	57	43
h	Br	4- NO ₂ -Ph	59	41
i	H	Pyridyl	54	46
j	Br	Pyridyl	57	43

Table 2

Indicating the results of anti-bacterial activity test conducted using compounds **4a-j**.

4a-j	Gram positive bacteria's		Gram negative bacteria's		
	<i>S.pyogen</i>	<i>B.subtilis</i>	<i>E.coli</i>	<i>Kl.pneumoniae</i>	<i>Ps.auregenosa</i>
a	16	16	13	16	17
b	27	23	23	19	18
c	14	19	17	21	14
d	16	16	16	13	15
e	16	18	14	17	16
f	16	16	20	19	14
g	14	16	18	21	15
h	15	15	16	12	13
i	22	16	17	19	16
j	14	18	19	13	15
Standard					
Ampicilline		13			
Solvent					
Methanol		Nil			

We were happy to note that all the compounds synthesized, namely, **4a-j**, exhibited better antibacterial activity than ampicillin, the standard used for the tests. The most active of the compounds was, 11-bromo-6-phenyl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4b**). The compound with pyridinyl moiety, 6-pyridin-3-yl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4i**), was also found to be significantly active. These excellent bioactivities, we believe, were due to the contribution of the heterocyclic sub-units incorporated and the steroidal framework, which is so very common in living systems. These results are presented in Table 2.

EXPERIMENTAL

Melting points reported are uncorrected. ir spectra were recorded on a Shimadzu FTIR-4200 spectrometer and pmr spectra were recorded on Varian EM-360L (60MHz), ho26rt-mercury 400 MHz spectrometer using TMS as an internal standard; cmr spectra were recorded on Varian Mercury plus 300 MHz. Mass spectra were recorded on GC-MSQP-1000. Elemental analyses were carried on Carlo Enra EA-1108 elemental analyzer. The homogeneity of compounds was checked by tlc on silica gel.

2,3-Dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one (**1a**) [15] and its 7-bromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one (**1b**) [16] derivative were synthesized as reported in the literature.

Synthesis of 3-Bromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one (**2a**).

A mixture containing 2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **1a** (1.96 g, 10 mmole) and *N*-bromo succinimide (1.78 g, 0.01 mol) along with a catalytic amount of benzoyl peroxide (20 mg) was refluxed in carbon tetrachloride (30 ml) for 4 hrs. The reaction mixture was then cooled and succinimide in the solid form was separated by filtration. The organic layer was then distilled to 1/4th the original volume and after over night refrigeration compound 3-bromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **2a** crystallized out from the reaction mixture. This compound [15] was obtained as white solid yield 2.63 (92%), mp 154 °C, ir (KBr): C=C 1560, 1600, C=O 1680 cm⁻¹, pmr: (CDCl₃): δ 3.5(m, 3H, CH and CH₂) and 7.1-8.0 (m, 6H, Ar).

Anal. Calcd. for C₁₃H₉BrO₂: % C, 56.35; H, 3.27; Br, 28.83. Found % C, 56.00; H, 2.98; Br, 28.60.

Synthesis of 3, 7-Dibromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one (**2b**).

Similar procedure was employed for the synthesis of 3,7-dibromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **2b**. 7-Bromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **1b** (2.77 g, 10 mmole) was used as starting material. 3,7-Dibromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **2b** was obtained as white solid yield 3.41g (96%), mp 220 °C, ir (KBr): C=C 1580, 1610, C=O 1685 cm⁻¹. pmr: (CDCl₃): δ 3.8(m, 3H, CH and CH₂) and 7.2-7.9(m, 5H, Ar).

Anal. Calcd. for C₁₃H₈Br₂O₂: % C, 43.86; H, 2.27; Br, 44.89. Found % C, 43.50; H, 1.98; Br, 44.62.

General Procedure for the Synthesis of 6-Aryl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4a-j**).

3-Bromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **2a** (2.77 g, 10 mmole), 3,7-dibromo-2,3-dihydro-4*H*-naphtho[1,2-*b*]pyran-4-one **2b** (3.56 g, 10 mmole) and 4-amino-3-mercapto-5-aryl-1,2,4-triazoles **3a-e** (10 mmole) was dissolved in DMF (5 ml). The temperature of this mixture was raised to 80-90 °C. The reaction was monitored with tlc. It was continued for 6 hr at which time the reaction mixture was cooled to room temperature. To this reaction mixture was added saturated Na₂CO₃ solution (10 ml). The reaction mixture was then stirred for 2 hr to neutralize the bromide salt formed. The solid obtained was collected by filtration and washed with water. The solid obtained was air dried and subjected to column chromatography over neutral alumina. The **5a/b** were eluted using pet ether: CHCl₃ 50:50 (30 ml each) system and after subsequent increase in polarity to CHCl₃: MeOH 99:1, 6-Aryl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine and its derivatives (**4a-j**) were obtained.

6-Phenyl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4a**).

This compound was obtained as pale yellow solid, mp 191-192 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (400 MHz DMSO) δ 4.6 (t, 1H, C(2a)-H J=12 & 10.8 Hz two doublets have merged together giving enhanced middle peak) 5.05 (dd, 1H, C(2)-H J=5.6 & 10.8Hz), 5.35 (dd, 1H, C(2)-H J= 5.6 & 12Hz), 7.5-7.6 (m, 3H, Ar) 7.7-7.8 (m, 6H, Ar), 7.9 (d, 1H, Ar J= 4Hz), 8.15 (d, 1H, C-14(H) Ar J=8.4 Hz.). cmr: (300MHz CDCl₃ TMS) δ 34.34(C(2a)), 67.27(C(2)), (Ar-C) 111.31, 120.58, 122.63, 122.77, 124.45, 125.83, 126.70, 127.76, 128.16(2C), 128.47(2C), 129.25, 130.19, 135.97, 139.45, 148.33, 152.16, 156.04. ms: m/z 370(M⁺), 371(M+1)⁺, 372(M+2)⁺.

Anal. Calcd. for C₂₁H₁₄N₄OS: % C, 68.09; H, 3.81; N, 15.12; O, 4.32; S, 8.66. Found % C, 67.80; H, 3.60; N, 14.90; O, 4.08; S, 8.42.

11-Bromo-6-Phenyl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4b**).

This compound was obtained as yellow solid, mp 154-156 °C, ir (KBr) 1590, 1610, 1620, 2960, 3010. pmr: (60 MHz DMSO) δ 4.7 (t, 1H, C(2a)-H) 5.1 (dd, 1H, C(2)-H), 5.30 (dd, 1H, C(2)-H), 7.5-7.62 (m, 3H, Ar) 7.7-7.8 (m, 5H, Ar), 7.8 (d, 1H, C-12(H) Ar J= 4Hz) 8.10 (d, 1H, C-14(H) Ar J=8.4 Hz.).

Anal. Calcd. for C₂₁H₁₃BrN₄OS: % C, 56.12; H, 2.90; Br, 17.82; N, 12.47; O, 3.56; S, 7.14. Found % C, 55.84; H, 2.71; Br, 17.66; N, 12.20; O, 3.32; S, 6.90.

6-[2'-Methoxyphenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**4c**).

This compound was obtained as pale yellow solid, mp 235-236 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (400 MHz DMSO) δ 3.8 (s, 3H, OCH₃) 4.4 (t, 1H, C(2a)-H J= 12.4 & 10.6 two doublets have merged together giving enhanced middle peak), 4.6(dd, 1H, C(2)-H J=5.4 & 10.6), 4.9(dd, 1H, C(2)-H J=5.4 & 12.4Hz), 7.0 (dd, 2H, Ar J=6.8Hz) 7.6(m, 3H, Ar), 7.8 (d, 1H, Ar J= 7.6Hz), 8.1(dd, 3H, Ar J=8.8Hz) 8.20 (d, 1H, C-14(H) Ar J= 8Hz). cmr: (300MHz CDCl₃ TMS) δ 34.30 (C(2a)), 55.12(C(2)), 67.20 (O-CH₂), (Ar-C) 111.29, 113.78(2C), 118.12,

120.42, 122.49, 122.68, 124.35, 126.54, 127.62, 129.07, 129.57(2C), 135.83, 138.89, 148.28, 151.97, 155.95, 160.92.

Anal. Calcd for $C_{22}H_{16}N_4O_2S$: % C, 66.00; H, 4.00; N, 14.00; O, 7.99; S, 8.00. Found % C, 65.72; H, 3.75; N, 13.78; O, 7.72; S, 7.78.

11-Bromo-6-[2'-methoxyphenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4d**).

This compound was obtained as brown solid, mp 160-161 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 3.8 (s, 3H, OCH₃), 4.5 (t, 1H, C(2a)-H) 4.8 (dd, 1H, C(2)-H), 5.1 (dd, 1H, C(2)-H), 7.5-7.8 (m, 7H, Ar), 7.8 (d, 1H, C-12(H) Ar J= 4Hz) 8.10 (d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd for $C_{22}H_{15}BrN_4O_2S$: % C, 55.12; H, 3.13; Br, 16.70; N, 11.69; O, 6.68; S, 6.69. Found % C, 54.85; H, 2.90; Br, 16.44; N, 11.42; O, 6.42; S, 6.42.

6-[4'-Chlorophenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4e**).

This compound was obtained as yellow solid, mp 209-210 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 4.8 (t, 1H, C(2a)-H) 5.0 (dd, 1H, C(2)-H), 5.2 (dd, 1H, C(2)-H), 7.2-7.8 (m, 8H, Ar) 7.9 (d, 1H, Ar J= 4Hz) 8.10 (d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd. for $C_{21}H_{13}ClN_4OS$: % C, 62.38; H, 3.22; Cl, 8.66; N, 13.86; O, 3.95; S, 7.92. Found % C, 62.15; H, 3.01; Cl, 8.50; N, 13.61; O, 3.67; S, 7.65.

11-Bromo-6-[4'-Chlorophenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4f**).

This compound was obtained as yellow solid, mp 184-185 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 4.6 (t, 1H, C(2a)-H) 5.01 (dd, 1H, C(2)-H), 5.15 (dd, 1H, C(2)-H), 7.4-7.8 (m, 7H, Ar) 7.94 (d, 1H, C-12(H) Ar J= 4Hz), 8.10 (d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd. for $C_{21}H_{12}BrClN_4OS$: % C, 52.17; H, 2.48; Br, 16.56; Cl, 7.25; N, 11.59; O, 3.31; S, 6.63; Found % C, 51.88; H, 2.22; Br, 16.31; Cl, 7.02; N, 11.34; O, 3.08; S, 6.36.

6-[4'-Nitrophenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4g**).

This compound was obtained as yellow solid mp 225-226 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (DMSO) pmr: (60 MHz DMSO) δ 4.6 (t, 1H, C(2a)-H) 5.05 (dd, 1H, C(2)-H), 5.35 (dd, 1H, C(2)-H), 7.5-7.7 (m, 8H, Ar), 7.9 (d, 1H, Ar J= 4 Hz), 8.15 (d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd. for $C_{21}H_{13}N_5O_3S$: % C, 60.72; H, 3.13; N, 16.87; O, 11.55; S, 7.71. Found % C, 60.46; H, 3.00; N, 16.62; O, 11.28; S, 7.48.

11-Bromo-6-[4'-nitrophenyl]-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4h**).

This compound was obtained as brown solid, mp 187-188 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 4.6 (t, 1H, C(2a)-H) 5.01 (dd, 1H, C(2)-H), 5.15 (dd, 1H, C(2)-H), 7.4-7.8 (m, 7H, Ar) 7.94 (d, 1H, C-12(H) Ar J= 4 Hz) 8.10 (d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd. for $C_{21}H_{12}BrN_5O_3S$: % C, 51.01; H, 2.43; Br, 16.19; N, 14.17; O, 9.71; S, 6.48. Found % C, 50.78; H, 2.18; Br, 15.92; N, 13.90; O, 9.48; S, 6.24.

6-Pyridin-3'-yl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4i**).

This compound was obtained as light brown solid, mp 170-172 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 4.58 (t, 1H, C(2a)-H) 5.95 (dd, 1H, C(2)-H), 5.15 (dd, 1H, C(2)-H), 7.4-7.8 (m, 8H, Ar), 8.0 (d, 1H, Ar J= 4 Hz) 8.2 (d, 1H, C-14(H) Ar J=8.4 Hz.). ms: m/z 371(M⁺), 372(M+1)⁺, 373(M+2)⁺.

Anal. Calcd. for $C_{20}H_{13}N_5OS$: % C, 64.69; H, 3.50; N, 18.87; O, 4.31; S, 8.63. Found % C, 64.42; H, 3.26; N, 18.60; O, 4.06; S, 8.36.

11-Bromo-6-Pyridin-3'-yl-2,2a-dihydro-naphtho[2',1'-5,6]pyrano[4,3-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4j**).

This compound was obtained as brown solid, mp 179-180 °C, ir (KBr) 1580, 1600, 1620, 2950, 3005. pmr: (60 MHz DMSO) δ 4.55 (t, 1H, C(2a)-H) 5.05 (dd, 1H, C(2)-H), 5.30 (dd, 1H, C(2)-H), 7.45-7.75 (m, 7H, Ar) 7.80 (d, 1H, C-12(H) Ar J= 4 Hz), 8.10(d, 1H, C-14(H) Ar J=8.4 Hz).

Anal. Calcd. for $C_{20}H_{12}BrN_5OS$: % C, 53.33; H, 2.66; Br, 17.77; N, 15.55; O, 3.55; S, 7.11. Found % C, 53.10; H, 2.46; Br, 17.49; N, 15.30; O, 3.32; S, 6.90.

7-Bromo-naphtho [1,2-b]pyran-4-one (**5b**).

This compound was obtained as white solid, mp 154 °C (decomp), ir (KBr): C=C 1600, 1620, C=O 1660cm⁻¹. pmr: (60Mhz) (DMSO) δ 6.5(d, 1H, CH, J = 8hz) and 7.1-8.2 (m, 6H, Ar and CH).

Anal. Calcd. for $C_{13}H_7BrO_2$: % C, 56.76; H, 2.56; Br, 29.05. Found % C, 56.40; H, 2.32; Br, 28.70.

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