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Synthesis of Some γ-Benzopyrone Derivatives as Analgesic Agents

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ABSTRACT

Considering the potential to be a lead molecule and having a wide variety of pharmacological activities like anti-inflammatory, anticancer, antihepatotoxic, antibacterial, antiviral etc., a series of bioactive γ-benzopyrone compounds were synthesized and analgesic activity was evaluated. The synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral studies. Some of the compounds synthesized i.e. 4c, 4d, 4g and 4h showed appreciable analgesic activity.

Keywords: Acylation, condensation, amino derivatives.

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INTRODUCTION

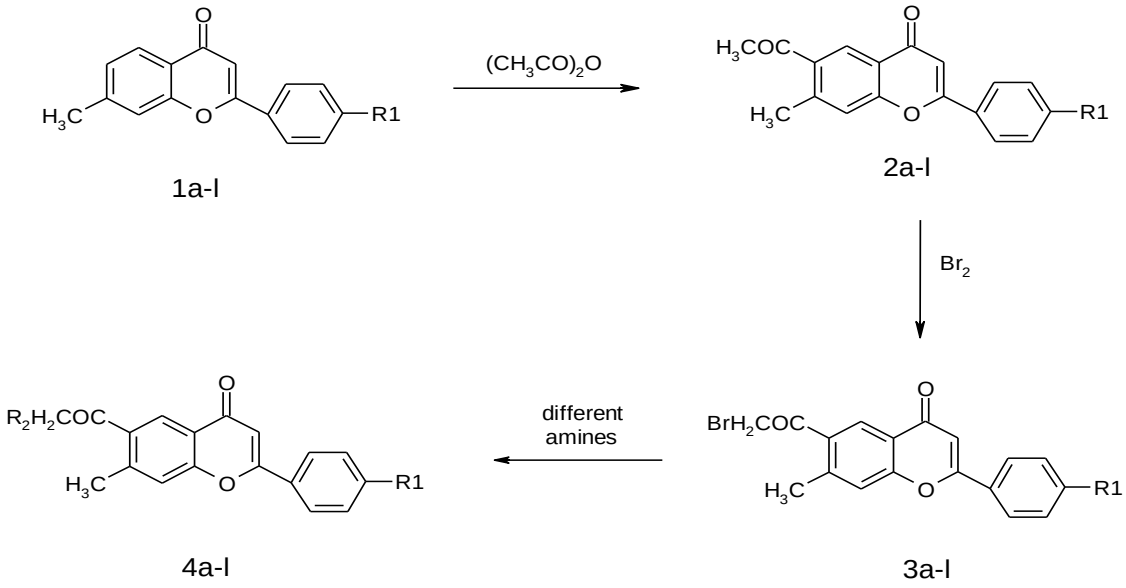
Drug discovery and development is a multidisciplinary process which requires a creative, innovative, highly systematic as well as rationalized approach. For centuries finding a lead nucleus had been a great challenge in medicinal chemistry. Once discovered, the lead molecules can then be optimized for their chemical stability, potency and therapeutic effectiveness. Oxygen containing heterocycles have a great potential to become a clinically useful drug. The benzopyrone ring system contains a benzene ring along with a pyran ring fused. The pyran ring is characterized by having a ketone group in its 4 or γ position and a π bond between C-2 and C-3. A number of scientific and technical reports which are satisfactory and statistically significant have highlighted the synthesis and utility with respect to their varied biological and pharmacological activities. Benzopyrones constitutes one of the major classes of natural products. They are a group of oxygen containing heterocycles, which occur in nature as flavones, isoflavones, neoflavones coumarins, etc. All these comprise major subclasses of a more broadly defined family of low molecular weight plant products known as the flavonoids**.** Depending on the type of lactone ring, benzopyrones are available as α-benzopyrones, β-benzopyrones and γ-benzopyrones. The chemistry of these has been reviewed extensively. Flavones, also known as the anthoxanthins, are yellow pigments, which occur in the plant kingdom. They occur naturally in free state or as glycosides or associated with the tannins. Chemically they are very closely related to the anthocyanins and occur as hydroxylated derivatives of 2-phenyl-4-chromone. The benzopyrones are reported to have a wide variety of effectiveness like antibacterial[1], antiviral[1], anti-inflammatory[2-6], antioxidant[7-10], antitumour[11] etc. There is a broad possibility for the synthesis of new compounds containing the amine moiety and amide linkage. The former containing electronegative nitrogen may have converted in-vitro into a quaternary ammonium compound, unless the substituents are very bulky in nature, which then facilitates the hydrophilic attitude of the molecule as well as its receptor binding. The latter i.e. the compounds containing amide linkage, may be hydrolyzed inside the body to liberate the active molecule which then can produce its actual pharmacological activity. Thus keeping considerations with all these facts, the aim of the present research study was to undertake a systematic approach to synthesize and evaluate some γ-benzopyrones derivatives.

MATERIALS AND METHOD

All the chemicals used were of analytical grade. The melting points were determined by open capillary tube method and are uncorrected. The progress of reaction and the purity of the

compounds were monitored and checked by using precoated Silica gel G plates; Benzene: ethyl acetate- 1:1 used as developing solvent; detections were carried out either in UV chamber or by using iodine vapour. The IR spectra were recorded using KBr discs in the region of 4000-400 cm^{-1} in a Shimadzu 8400S FTIR spectrophotometer. NMR spectra were recorded using TMS as internal standard on a Brukar Spectrospin 200 spectrometer. Mass spectral analysis was carried out by using JEOL GC mate instrument. The necessary ethical clearance was obtained for this study from the Institutional Animal Ethics Committee of M.M.U College of Pharmacy, K.K. Doddi, Ramanagara- 562159. Karnataka.

SCHEME OF SYNTHESIS



Synthesis of 6-acetyl-7-methyl-2-(4-chlorophenyl) benzopyran-4-one (2a)

0.01 mol of γ-benzopyrone (1a) was added to 30 ml of nitrobenzene. To this added 0.01 mol of acetic anhydride and freshly powdered 0.022 mol of anhydrous aluminium chloride and then the reaction mixture was heated in an oil bath for around 4 hours. The flask was then removed and cooled. To this 75 gm of crushed ice was added followed by 4 ml of concentrated hydrochloric acid. The product obtained was filtered and recrystallized from 95% ethanol.

Preparation of 6-bromoacetyl-7-methyl-2-(4-chlorophenyl) benzopyran-4-one (3a)

Around 50 ml of glacial acetic acid was taken in a beaker and then added 0.01 mol of acetylated γ-benzopyrone (2a); the reaction mixture kept on a magnetic stirrer. To this solution added bromine drop wise over a period of 1.5 hours with continuous stirring. The resulting solution was continued to stir for further 6 hours; till then the evolution of hydrogen bromide ceases. The resulting solution was then poured on around 250 gm of crushed ice. Crystals were collected by filtration. The product was then recrystallized from 50% alcohol.

Synthesis of amino derivatives of 6-bromoacetyl-7-methyl-2-(4-chlorophenyl) benzopyran-4-one (4a-l)

To a solution of bromo derivative of γ-benzopyrone (3a) (0.01 mol) in absolute alcohol (25 ml) was added the amine (0.01 mol) and the mixture was heated under reflux for about 2 hours on water bath. The solution was kept aside for another 6 hours. A crystalline solid was separated out on standing the above solution overnight in cold condition. The solid was filtered, washed repeatedly with cold water and dried.

Analgesic activity

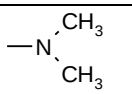
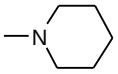
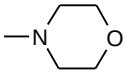
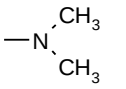
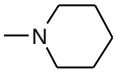
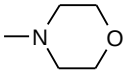
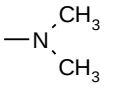
Tail immersion method using albino rats was used to check out the analgesic activity of the synthesized compounds. In this method the tail of a rat is dipped into the water up to a certain mark maintained at a temperature of 55^0C. The time taken to withdraw the tail from hot water is considered as the time for creating analgesia. The basal reaction time was noted for all animals by observing the withdrawal time of the tail. To the first group injected DMSO (control), the second group with diclofenac (standard) and the other groups were injected with different derivatives of γ-benzopyrones at a dose of 68.75 mg/kg body weight. Then at 0, 15, 30, 60 and 120 minutes interval the reaction times of the animals in hot water were noted after the drug administration and the data are produced in table-2. As the reaction time increased with drugs 12 seconds was taken as cut off time.

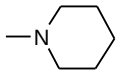
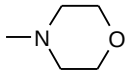
RESULTS AND DISCUSSION

The title compounds (4a-l) were synthesized in an appreciable yield after condensing bromo derivatives of substituted γ-benzopyrones (3a-l) with different amines namely ptrrolidine, dimethyl amine, piperidine and morpholine. The structures of all the synthesized compounds were confirmed by their IR, NMR and Mass spectral analysis. The IR spectra (4a-l) showed the presence of absorption bands around 3027-3083 cm^{-1} for C-H stretching aromatic and 2847-2932 for C-H stretching aliphatic. The appearance of an absorption band in the IR spectra of 3a-l represents the C-Br stretching, confirmed the bromination of 2a-l. The condensation of the suitable amines with 3a-l was confirmed by the disappearance of this peak and the appearance of C-N absorption band around 1092-1179 cm^{-1} of compounds 4a-l. The NMR spectra of the title compounds (4a-l) showed characteristic multiplet peaks for aromatic protons around δ 7.4-8.4. The appearance of a sharp singlet in the NMR spectra of 4a-l around δ 6.7-7.2 confirmed the presence of the C-3 proton; because of the high deshielding effect exerted by the doubly bonded electrons moves the signal for non-aromatic proton to be appeared at the downfield value.

Further analysis of the NMR spectra reveled that the 7–CH_3 protons were appeared at the region of δ 2.3-2.6, a value rather higher than its normal value where alkyl protons usually appears; this is because that the 7-CH_3 group is attached directly with the aromatic ring, thus more deshielding effect made these protons to be appeared at a little downfield. The alkyl protons of 6-acetyl group of compounds 4a-l appeared at around δ 3; this deshielding took place because the -CH_2- group is clubbed between C=O and the amino nitrogen, thus the dual electronegative effect of carbonyl group as well as the nitrogen forced these two methylene protons to appear at somewhat downfield. In amine molecules there are two kinds of protons; one on carbon atoms directly attached to the nitrogen or oxygen and the other where the carbons are not directly attached to the nitrogen or oxygen. Thus in the former case, due to an obvious reason of electronegativity of nitrogen and oxygen, the protons appeared at a relatively higher δ value compared to normal alkyl protons. The Mass spectra of the compounds gave the characteristic M+H peak from which the molecular weights of the compounds were confirmed.

Table-1. Physical data of synthesized derivatives

Compound code	R1	R2	Mol. Formula	Mol. Wt.	M.P (^{0}C)	R_f value	Yield (%)
4a	-Cl		$C_{22}H_{20}ClNO_3$	381.86	182	0.72	72
4b	-Cl		$C_{20}H_{18}ClNO_3$	355.82	165	0.64	67
4c	-Cl		$C_{23}H_{22}ClNO_3$	395.89	150	0.74	59
4d	-Cl		$C_{22}H_{20}ClNO_4$	397.86	140	0.72	68.5
4e	-NO_2		$C_{22}H_{20}N_2O_5$	392.42	185	0.66	63
4f	-NO_2		$C_{20}H_{18}N_2O_5$	366.38	167	0.62	64
4g	-NO_2		$C_{23}H_{22}N_2O_5$	406.44	177	0.71	48
4h	-NO_2		$C_{22}H_{20}N_2O_6$	408.41	195	0.73	65
4i	-Br		$C_{22}H_{20}BrNO_3$	426.31	189	0.74	71
4j	-Br		$C_{20}H_{18}BrNO_3$	400.28	201	0.71	65

4k	-Br		$C_{23}H_{22}BrNO_3$	440.34	176	0.65	63
4l	-Br		$C_{22}H_{20}BrNO_4$	442.31	189	0.74	63.5

4a IR (KBr, cm^{-1}): 3065 C-H str aromatic, 2850 C-H str aliphatic, 1646 C=O ketone, 1567 C=C str, 1337 C-H bending aliphatic, 1129 C-N vibration, 850 C-H bending aromatic, 764 C-Cl str. ^{1}H NMR (δ): 1.8-2.1 4H m alkyl H, 2.5-2.6 3H s alkyl H, 2.9 2H s alkyl H, 3.5-3.7 4H m alkyl H, 6.8 1H s C-3 H, 7.6-7.8 4H m Ar H, 8.1-8.3 2H m Ar H. Mass (M+H): 382.86

4b IR (KBr, cm^{-1}): 3027 C-H str aromatic, 2930 C-H str aliphatic, 1679 C=O ketone, 1592 C=C str, 1338 C-H bending aliphatic, 1092 C-N vibration, 829 C-H bending aromatic, 700 C-Cl str. ^{1}H NMR (δ): 2.3-2.4 3H s alkyl H, 2.5-2.7 6H alkyl H, 3.1 2H s alkyl H, 7.0 1H s C-3 H, 7.6-7.8 4H m Ar H, 8.0-8.1 2H m Ar H. Mass (M+H): 356.82

4c IR (KBr, cm^{-1}): 3064 C-H str aromatic, 2870 C-H str aliphatic, 1638 C=O ketone, 1512 C=C str, 1374 C-H bending aliphatic, 1125 C-N vibration, 851 C-H bending aromatic, 764 C-Cl str. ^{1}H NMR (δ): 2.0-2.2 6H m alkyl H, 2.4 3H s alkyl H, 2.7-2.8 4H m alkyl H, 3.2 2H s alkyl H, 7.2 1H s C-3 H, 7.8-8.0 4H m Ar H, 8.2-8.3 2H Ar H. Mass (M+H): 395.89

4d IR (KBr, cm^{-1}): 3083 C-H str aromatic, 2932 C-H str aliphatic, 1679 C=O ketone, 1576 C=C str, 1387 C-H bending aliphatic, 1179 C-N vibration, 832 C-H bending aromatic, 755 C-Cl str. ^{1}H NMR (δ): 2.3-2.4 3H s alkyl H, 3.4-3.5 2H s alkyl H, 3.9-4.2 8H m alkyl H, 6.7 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-7.9 2H Ar H. Mass (M+H): 398.86

4e IR (KBr, cm^{-1}): 3064 C-H str aromatic, 2848 C-H str aliphatic, 1645 C=O ketone, 1566 C=C str, 1466 C-NO_2 str, 1376 C-H bending aliphatic, 1128 C-N vibration, 849 C-H bending aromatic. ^{1}H NMR (δ): 1.8-2.1 4H m alkyl H, 2.5-2.6 3H s alkyl H, 2.9-3.0 2H s alkyl H, 3.4-3.7 4H m alkyl H, 6.8 1H s C-3 H, 7.4-7.7 4H m Ar H, 8.0-8.1 2H Ar H. Mass (M+H): 393.42

4f IR (KBr, cm^{-1}): 3064 C-H str aromatic, 2850 C-H str aliphatic, 1645 C=O ketone, 1565 C=C str, 1461 C-NO_2 str, 1375 C-H bending aliphatic, 1127 C-N vibration, 852 C-H bending aromatic. ^{1}H NMR (δ): 2.3-2.4 3H s alkyl H, 2.6-2.7 6H alkyl H, 3.2 2H s alkyl H, 6.8 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-7.9 2H Ar H. Mass (M+H): 367.38

4g IR (KBr, cm^{-1}): 3061 C-H str aromatic, 2847 C-H str aliphatic, 1650 C=O ketone, 1569 C=C str, 1464 C-NO_2 str, 1375 C-H bending aliphatic, 1128 C-N vibration, 850 C-H bending aromatic. ^{1}H NMR (δ): 1.9-2.2 6H m alkyl H, 2.3-2.4 3H s alkyl H, 2.7-2.8 4H m alkyl H, 3.2 2H s alkyl H, 6.8 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-7.9 2H Ar H. Mass (M+H): 407.43

4h IR (KBr, cm^{-1}): 3061 C-H str aromatic, 2848 C-H str aliphatic, 1646 C=O ketone, 1567 C=C str, 1465 C-NO_2 str, 1376 C-H bending aliphatic, 1128 C-N vibration, 850 C-H bending aromatic. ^{1}H NMR (δ): 2.3-2.4 3H s alkyl H, 3.4-3.5 2H alkyl H, 3.9-4.2 8H m alkyl H, 6.7 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-7.9 2H Ar H. Mass (M+H): 409.41

4i IR (KBr, cm^{-1}): 3055 C-H str aromatic, 2870 C-H str aliphatic, 1672 C=O ketone, 1548 C=C str, 1307 C-H bending aliphatic, 1143 C-N vibration, 858 C-H bending aromatic, 694 C-Br str. ^{1}H NMR (δ): 1.8-2.1 4H m alkyl H, 2.5-2.6 3H s alkyl H, 2.9-3.0 2H s alkyl H, 3.4-3.7 4H m alkyl H, 6.8 1H s C-3 H, 7.4-7.7 4H m Ar H, 8.0-8.1 2H Ar H. Mass (M+H): 427.31

4j IR (KBr, cm^{-1}): 3064 C-H str aromatic, 2849 C-H str aliphatic, 1645 C=O ketone, 1565 C=C str, 1375 C-H bending aliphatic, 1127 C-N vibration, 851 C-H bending aromatic, 603 C-Br str. ^{1}H NMR (δ): 2.2 3H s alkyl H, 2.4-2.5 6H alkyl H, 3.1 2H s alkyl H, 6.9 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-7.9 2H Ar H. Mass (M+H): 401.28

4k IR (KBr, cm^{-1}): 3070 C-H str aromatic, 2847 C-H str aliphatic, 1645 C=O ketone, 1568 C=C str, 1310 C-H bending aliphatic, 1129 C-N vibration, 850 C-H bending aromatic, 605 C-Br str. ^{1}H NMR (δ): 1.9-2.2 6H m alkyl H, 2.3-2.4 3H s alkyl H, 2.7-2.8 4H m alkyl H, 3.2 2H s alkyl H, 6.8 1H s C-3 H, 7.8-8.0 4H m Ar H, 8.2-8.4 2H Ar H. Mass (M+H): 441.34

4l IR (KBr, cm^{-1}): 3068 C-H str aromatic, 2848 C-H str aliphatic, 1645 C=O ketone, 1566 C=C str, 1311 C-H bending aliphatic, 1128 C-N vibration, 850 C-H bending aromatic, 604 C-Br str. ^{1}H NMR (δ): 2.3-2.4 3H s alkyl H, 3.4-3.5 2H s alkyl H, 3.9-4.2 8H m alkyl H, 6.7 1H s C-3 H, 7.4-7.6 4H m Ar H, 7.8-8.0 2H Ar H. Mass (M+H): 443.31

It was worthy to note that some of the synthesized compounds showed significant analgesic activity; compounds 4c, 4d, 4g and 4h showed very good analgesic activity. Other derivatives were weakly or moderately active.

Table-2. Analgesic activity of the synthesized compounds.

Compound code	0 min	15 min	30 min	60 min	120 min
Control	2.00 ± 0.204	2.05 ± 0.210	2.00 ± 0.210	2.1 ± 0.210	2.4 ± 0.408
Std.	2.14 ± 0.239	3.25 ± 0.144***	4.87 ± 0.125***	6.49 ± 0.125***	6.6 ± 0.204***
4a	2.14 ± 0.144	2.39 ± 0.125	3.15 ± 0.288	3.85 ± 0.204	4.38 ± 0.166*
4b	2.00 ± 0.166	2.51 ± 0.125	3.57 ± 0.288	3.98 ± 0.204*	4.43 ± 0.166*
4c	2.00 ± 0.166	3.18 ± 0.144***	4.92 ± 0.114***	5.32 ± 0.288***	5.68 ± 0.125***
4d	2.78 ± 0.166	3.05 ± 0.288***	4.42 ± 0.166***	5.21 ± 0.133***	5.43 ± 0.125***
4e	1.98 ± 0.301	2.42 ± 0.144	3.21 ± 0.239	4.35 ± 0.204*	5.19 ± 0.125**
4f	1.95 ± 0.125	2.39 ± 0.166	3.35 ± 0.288	3.95 ± 0.204*	4.35 ± 0.301*
4g	2.01 ± 0.125	3.84 ± 0.144***	5.0 ± 0.204***	5.8 ± 0.166***	6.12 ± 0.216***
4h	2.14 ± 0.144	3.83 ± 0.288***	5.01 ± 0.239***	6.33 ± 0.127***	6.24 ± 0.274***
4i	2.12 ± 0.133	2.41 ± 0.125	2.61 ± 0.288	2.83 ± 0.204	2.75 ± 0.239

4j	2.15 ± 0.239	2.48 ± 0.144	2.61 ± 0.125	3.10 ± 0.288	3.21± 0.346
4k	1.95 ± 0.204	2.38 ± 0.144	3.41 ± 0.125*	4.15 ± 0.239*	4.99 ± 0.288**
4l	1.98 ± 0.288	2.45 ± 0.239	3.32 ± 0.204*	4.10 ± 0.144*	4.95 ± 0.166**

Statistical significance was analyzed by ANOVA followed by post-parametric Dunnet test. ***Extremely significant, **Highly significant, *Significant. n = 6

CONCLUSION

The results of the analgesic screening revealed that substituted γ-benzopyrones condensed with different amines may be investigated further for future drug development, although thorough evaluations regarding their pharmacokinetics are required to optimize these compounds.

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