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Research Article

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Ultrasound Enabled Synthesis of Few Coumarins and a Study of Lipophilicity

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ABSTRACT

The objective of the present investigation was to synthesize nitro and bromo derivatives of 4-hydroxycoumarins, 4,7-dihydroxycoumarins and their C-methylated derivatives by ultrasound irradiation and assess the lipophilicity of these coumarin derivatives by shake-flask method with octanol-water as solvent. Log P values were also calculated with HYPERCHEM software. The results indicated that 4,7-dimethylcoumarin and 6-bromo-4,7-dimethylcoumarin possess the highest lipophilicity. The lipophilic value calculated by shake flask method reveals that 4-methyl 7-hydroxy-6-nitrocoumarin, 4-methyl 7, 8-dihydroxy-6-nitrocoumarin and 6-bromo-4,7-dihydroxycoumarin have high lipophilic value.

Keywords: Coumarin derivatives; Lipophilicity; Shake flask method; Octanol-water system

Abbreviation: TLC: Thin Layer Chromatography; UV: Ultraviolet Spectroscopy; IR: Infra-Red; O/W: Octanol Water System; Log P: Partition coefficients

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INTRODUCTION

A notable part of research carried out in chemistry is devoted to the study of heterocyclic compounds. Of the large number of heterocyclic compounds, coumarins are known for more than a century because of their unique pharmacological properties. Many of the coumarin derivatives are known to be physiologically active and exhibit a wide variety of application in drug discovery because of their biological activities [1-3]. Coumarins are reported to act as anticonvulsant, anti-bacterial, anti-insecticidal, anti-inhibitory agents and oral anticoagulants. Coumarins also possess anthelmintic, hypnotic and insecticidal activities [4-16]. Coumarin derivatives can be synthesized by conventional methods or by green methods. Green chemistry is "the use of techniques and methodologies that reduce or eliminate the use or generation of feedstock, products, by-products, solvents and reagents that are hazardous to human health and the environment" [17]. It is a micro scale chemistry method which is a laboratory based, environmentally safe and a pollution-prevention approach. To create an ecofriendly and non-toxic environment, we aimed to synthesize coumarin by ultrasound irradiation [18-21]. Recently, Ultrasound aided synthesis has attained an impressive development in the field of chemical synthesis, including material science, aerosols, food chemistry and other research areas.

One of the most important parameters describing the pharmacokinetic aspects of drug action is lipophilicity [22-24]. The term lipophilic literally means "oil loving", and lipophilicity is a measure of the degree to which a given molecule prefers hydrophobic non-polar environments to water. The most common experimental measure of lipophilicity is the log of the partition coefficient for a solute distributing itself between water and some organic solvent such as 1-octanol or chloroform [25-27]. Partition coefficients (Log P) are usually determined by the shake-flask method [28-31]. Octanol and water are widely accepted as the best two-phase system to model the partitioning

between biomass and water. The development of accurate prediction methods for hydrophobicity depends on the availability of measurements on compounds with unique fragments.
In consideration of the biological activity of coumarins and their applications in drug discovery, we aimed to synthesize nitro and bromo derivatives of coumarins by ultrasound irradiation and to determine the lipophilicity of these coumarins by shake flask method using octanol-water system. The values were then compared with the log P values obtained from HYPERCHEM software [32,33].

MATERIALS AND METHODS

Experimental Section

All reactions were monitored by TLC (Merck Silica gel) using petroleum ether, chloroform and ethyl acetate as developing solvents. The yields reported are calculated from analysis of the crude reaction mixtures**.** Melting points were recorded on an Expo-DI/QC/M/107 melting point apparatus and are uncorrected. Sonication was carried out using Ultrasonics 230 V AC, 50 Hz. Infrared spectrum was recorded on Bruker-FTIR model. UV spectra were recorded on a double beam spectrophotometer-systronics-2202 model. The compounds were detected by Hitachi UV lamp – F8T5 (254 nm).

Ultrasound Aided Synthesis of Coumarins

Synthesis of 4–hydroxycoumarin (P1):

A mixture of phenol (4.5 ml), malonic acid (5.2 g), fused zinc chloride (18.5 g) and phosphorus oxychloride (15 ml) was irradiated in an ultrasonic bath. The progress of the reaction was monitored by TLC. The product was cooled and decomposed with ice water and allowed to stand. The resulting 4-hydroxy coumarin was dissolved in 10% Sodium Carbonate and acidified. At about neutral point some oily by product separated out and was removed. Acidification of the remaining solution gave 4-hydroxy coumarin. On crystallisation from dilute alcohol pure 4-hydroxycoumarin was obtained**.**

Synthesis of 4-methyl 7-hydroxycoumarin (P2):

A solution of resorcinol (11 g) in ethyl acetoacetate (13 ml) is added to cold concentrated sulphuric acid (100 ml) and is then irradiated in an ultrasonic bath. The reaction mixture was kept for 20 hours at room temperature and poured with vigorous stirring onto crushed ice. The separated product was filtered, washed with water and crystallized from dilute alcohol.

Synthesis of 4, 7-dimethylcoumarin (P3):

A mixture of p-cresol (21 ml) and ethyl acetoacetate (26 ml) in sulphuric acid (50 ml) was irradiated in an ultrasonic bath. The reaction mixture was then cooled and poured into ice water. The product was filtered, washed with water, dried and then recrystallised from dilute alcohol to obtain the pure product.

Synthesis of 4, 7-dihydroxycoumarin (P4):

A mixture of resorcinol (5 g), malonic acid (5.2 g), fused zinc chloride (18.5 g) and phosphorous oxychloride (15 ml) was irradiated in an ultrasonic bath. After the reaction was complete as monitored by TLC, the crude product obtained from the reaction was recrystallised from hot water to obtain the pure product.

Synthesis of 4-methyl 7, 8-dihydroxycoumarin (P5):

A mixture of phloroglucinol (20 ml) and ketoester (21 ml) was irradiated in an ultrasonic bath in the presence of concentrated sulphuric acid. After completion of the reaction, the reaction mixture was cooled at room temperature and poured onto crushed ice. The solid product obtained was filtered off, washed with ice-cold water and recrystallized from hot ethanol to obtain the pure product.

Ultrasound aided synthesis of nitrocoumarins (P 1-5 N):

Coumarin derivative (100 mg) was mixed with acetic acid (3 ml) and concentrated nitric acid (2 ml) and is then irradiated in an ultrasonic bath. The progress of the reaction was monitored using TLC. The reaction mixture was cooled and then poured onto ice water. The product obtained was filtered, washed with water and then dried.

Ultrasound aided synthesis of bromocoumarins (P 1-5 B):
A mixture of coumarin derivative (100 mg) and bromine in glacial acetic acid was irradiated in an ultrasonic bath. The completion of the reaction was monitored using TLC after which the reaction mixture was poured into ice water and the solid formed was filtered off, dried and is then recrystallized from alcohol to get the pure product.

Theoretical Determination of Lipophilicity
After the preparation of various coumarins by using ultrasound irradiation, theoretical prediction of these samples/drugs was carried out using Hyperchem 7.0 software.

Experimental Determination of Lipophilicity
After the preparation of various coumarins by using ultrasound irradiation, the experimental analysis was carried out using Shake- Flask Method. A sample of 10 mg of coumarin samples was dissolved in 1-octanol in a 25 ml volumetric flask, which was then pre-saturated with water 24 hr prior to use. A sample solution of 0.5 ml was transferred to a 10 ml calorimetric tube. The octanol pre-saturated water was then added to the calorimetric tube. The resulting two-phase mixture was kept in a 25^{o}C water bath for 40 minutes, strongly shaken once in 5 min for attainment of equilibrium between the two phases. This sample (1 ml) was centrifuged for 10 minutes and the concentration of coumarin in the organic phase was analyzed in a UV/ VIS spectrophotometer. From the data obtained using UV/ VIS spectrophotometer, the concentration of coumarins in the organic phase and the aqueous phase is determined. The experimental value of log P was then calculated using the relationship

$$P = \frac{Concentration\ of\ drug\ in\ Octanol\ Phase}{Concentration\ of\ drug\ in\ Aqueous\ Phase}$$

$$Log\ P = \log(\frac{[C]Octanol}{[C]water})$$

RESULTS AND DISCUSSION

The results of the present work are presented in Tables 1 and 2. It can be envisaged from the data obtained from the Table 1, the time of synthesis of all the coumarins was considerably reduced under ultrasound irradiation showing the feasibility of the present method. The yield of 4-methyl 7-hydroxycoumarin (92%) and 4-methyl 7, 8-dihydroxycoumarin (95%) is very high compared to all other coumarins synthesized under ultrasound irradiation. But the time required for the synthesis of 4-methyl 7, 8-dihydroxycoumarin (122 mins) is high compared to 4-methyl 7-hydroxycoumarin (65 mins). The yield of 4-methyl-7-hydroxy-6-nitrocoumarin (83%) and 4-methyl- 7, 8-dihydroxy6-nitrocoumarin (85%) is high compared to other nitro substituted coumarins. The time required for the synthesis of 4-methyl 7 hydroxy-6-nitrocoumarin (15 mins) is dramatically reduced compared to 4-methyl -7, 8-dihydroxy-6-nitrocoumarin (25 mins). The yield of 6-bromo- 4-methyl 7-hydroxycoumarin (83%) and 4-methyl -7, 8 –dihydroxy 6-bromo coumarin (88%) is more compared to other bromo derivatives of coumarins synthesized under ultrasound irradiation. The time required for the synthesis was also comparatively less. It was observed from the results, that the nitro derivative of 4-hydroxycoumarin and 4, 7-dihydroxycoumarin (yield less) was not formed due to the acidity conferred on the molecule by the lactone ring whereas the introduction of methyl groups gradually weakens this acidity and makes the molecule more susceptible to the action of nitric acid (high yield). It was also found that the bromo derivative of 4-hydroxycoumarin (yield less) and 4, 7-dihydroxycoumarin is also not formed because of the bulky group present on the molecule and also due to the electron withdrawing nature of the substituent. The IR spectra recorded for all the synthesized compounds confirms the formation of the coumarin moiety and the IR spectral assignments are furnished in Table 2. The highest lipophilic value as calculated using HYPERCHEM software was obtained for 4,7-dimethylcoumarin and 6- Bromo- 4,7 dimethylcoumarin. The lipophilic value calculated by shake flask method (Table 1) reveals that 4-methyl 7-hydroxy -6-nitrocoumarin, 4-methyl-7,8-dihydroxy- 6-nitrocoumarin and 6- bromo- 4, 7-dimethylcoumarin have high lipophilicity compared to other coumarins. From these data, it was suggested that these compounds can be intended for oral administration since the log $P_{o/w}$ value is less than 5 [34]. Moreover, the lipophilic value calculated using HYPERCHEM software (0.67) and by shake flask method (0.41) is in good agreement for bromo derivative of 4,7- dimethyl coumarin.
Besides these, the lipophilic value of 6-bromo-4-methyl-7-hydroxy coumarin and 6-bromo-4,7-dimethylcoumarin calculated using HYPERCHEM software and by shake flask method is comparable as seen from Table 1. From the above discussion, it may be concluded that ultrasound aided synthesis seems to be a versatile method for the preparation of various coumarins particularly 4– methyl-7- hydroxy coumarin and 4-methyl-7, 8- dihydroxy

coumarin and its bromo and nitro derivative. It is clear from the results that the lipophilic value calculated using shake flask method agrees quite well with the HYPERCHEM software.

Table 1: Time and yield of coumarin derivatives synthesized under ultrasound

S No	Compounds	Code	Reaction Time (minutes)	Yield (%)	Melting Point (°C)	Log P (Experimental)	Log P (Theoretical)
1	4-hydroxycoumarin	P1	105	80	160	-0.29	-0.71
2	4-methyl-7-hydroxycoumarin	P2	65	92	108-112	-0.39	-0.56
3	4,7- dimethylcoumarin	P3	93	76	163-165	-0.87	0.62
4	4,7-dihydroxycoumarin	P4	156	68	155	-0.66	-1.73
5	4-methyl-7, 8-dihydroxycoumarin	P5	122	95	205	-0.41	-1.58
6	4-hydroxy-6-nitrocoumarin	P1N	55	-	-	-	-4.88
7	4-methyl-7-hydroxy -6-nitrocoumarin	P2N	15	83	182	0.04	-4.72
8	4,7-dimethyl-6-nitrocoumarin	P3N	40	62	80	-0.29	-3.55
9	4,7-dihydroxy-6-nitrocoumarin	P4N	40	15	155	-	-5.9
10	4-methyl-7, 8 dihydroxy - 6-nitrocoumarin	P5N	25	85	155-157	0.45	-5.75
11	6- bromo- 4-hydroxycoumarin	P1B	7	45	159	-0.6	-0.66
12	6- bromo- 4-methyl-7-hydroxycoumarin	P2B	80	83	210	-0.58	-0.5
13	6- bromo- 4,7 dimethylcoumarin	P3B	100	78	134-135	0.41	0.67
14	6- bromo- 4,7-dihydroxycoumarin	P4B	150	-	-	-	-1.68
15	6- bromo- 4-methyl -7,8-dihydroxycoumarin	P5B	60	88	175	-0.79	-1.53

Table 2: IR spectra of synthesised coumarins

S.No	Compounds	C-H Stretching	Hydroxy Group	Lactone C=O Str	C-O-C linkage	C-NO_{2str}	C-Br str
1	P1	2970	3460	1739	1220		
2	P2	2999	3484	1733	1214		
3	P3	2965		1706	1227		
4	P4	3018	3400	1737	1222		
5	P5	3076	3543	1723	1290		
6	P1N						
7	P2N	2971	3583	1734	1212	1575	
8	P3N	3069		1724	1201	1526	
9	P4N	315	3366	1733	1211	1540	
10	P5N	3081	3250	1735	1289	1531	
11	P1B	2952	3383	1735	1211		602
12	P2B	2362	3271	1715	1195		577
13	P3B	2922		1713	1237		675
14	P4B						
15	P5B	2976	3238	1715	1279		666

CONCLUSION

In this paper, from the results obtained, we conclude that various Bromo and Nitro substituted coumarins synthesized by ultrasound irradiation shows that the time of synthesis was considerably reduced from few minutes to less than three hours for these coumarins compared to the conventional method. The lipophilic value (log P) calculated by HYPERCHEM software suggests that 4,7-dimethylcoumarin, 6-bomo-4,7 dimethylcoumarin have highest lipophilicity. The lipophilic value (log P) calculated by shake flask method reveals that 4-methyl 7-hydroxy -6-nitrocoumarin, 4-methyl 7, 8-dihydroxy-6-nitrocoumarin and 6-bromo-4, 7-dihydroxycoumarin have high lipophilic value compared to other coumarins. The lipophilic value of 6-bromo-4-methyl-7-hydroxy coumarin and 6-bromo-4,7-dimethylcoumarin calculated using HYPERCHEM Software and shake flask method is comparable. The lipophilic value calculated using shake flask method agrees quite well with the HYPERCHEM software.

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