Chapter III

Section A

Synthesis of benzopyrazine or quinoxaine derivative of friedelin in water catalyzed by SDS

1. Introduction

Benzopyrazines or quinoxalines are ubiquitous heterocyclic units in pharmaceuticals and bioactive natural products.[89-92] They are used as pharmaceuticals and antibiotics such as echinomycin, levomycin and actinoleutin which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors.[89-91] Antitumoral properties of quinoxaline compounds have also been investigated. Beside these, they are well known for their application in dyes[93] as an efficient electroluminescent materials[94] in organic semiconductors[95] as building blocks for the synthesis of anion receptors[96] as cavitands[97,98] dehydroannulenes[99] and DNA cleaving agents.[100,101] Conventionally, quinoxalines are synthesized by a double condensation reaction involving a dicarbonyl precursor and *o*-phenylenediamine.[102,103] Due to the highly reactive nature of the dicarbonyls, alternative routes have been proposed recently.[104] Antoniotti and Donach have reported one of these methods to synthesize quinoxalines from epoxides and ene-1,2-diamines.[104] Active manganese oxide and molecular sieves in combination or manganese oxides in combination with microwaves have also been used in producing quinoxalines.[105,106] These processes, however, require excessive amounts of corrosive manganese oxide as stoichiometric oxidants and scaling them up for industrial processes can lead to the formation of large amounts of toxic waste leading to environmental issues. In additional studies, Robinson and Taylor reported a homogeneous catalytic process utilizing $Pd(OAc)_2$, $RuCl_2$ $(PPh_3)_2$ to synthesize quinoxalines from hydroxy ketones[107] and recently a copper catalyzed oxidative cyclization process has been reported.[108] An improved ruthenium catalyzed direct approach to synthesize quinoxalines from diols and *o*-diamines has also been reported.[109] These processes suffer from the major drawback that the catalysts are expensive, toxic and cannot be recovered and reused. In addition to the above catalytic methods, synthesis

of quinoxalines using zeolites[110-113] microwave[114-115] and solid supports[116-118] has also been reported. Nevertheless, these methods suffer from unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors and harsh reaction conditions, which limit their use as environmentally friendly protocol. In addition most of the reported methods are not recommended as a clean protocol.

Although very few of the recent reports have claimed α-bromoketones as an equivalent safe chemical precursor of α-hydroxyketones, epoxides or dicarbonyls as reaction partners of *o*-phenylenediamine to prepare quinoxalines[119-121] they involved the use of either $HClO_4$-SiO_2 or TMSCl as catalyst. Although useful, $HClO_4$ has huge hazardous nature than its potential usefulness, whereas those catalyzed by TMSCl needs higher temperature, with lower yield of the desired products not satisfying the principles of green chemistry protocol in contemporary science as well as their acceptance for industrial applications.

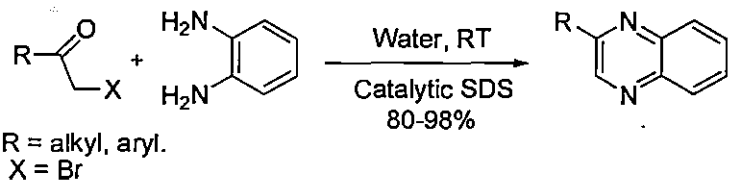
In this context the development of an alternative route to quinoxaline from less reactive α-bromoketones in aqueous medium was felt necessary not only due to the increased regulatory pressure focusing on organic solvents, but also because of the emphasis given towards the development of green protocol for organic synthesis nowadays.

The use of water as a medium for organic synthesis is one of the latest challenges in organic synthesis. Reactions in water emerged as a useful alternative route for several organic reactions owing to many of its potential advantages such as safety, economy and friendly towards catalytic and stereoselective processes and more importantly of environmental concern[121-122] and the progress has been dramatic. Additionally, water facilitates ion separation through salvation which often results in altered behavior of reactants in an aqueous environment. Keeping these above facts in mind, the present author has recently tested water as a solvent in many of his ongoing studies towards organic syntheses and transformative reactions. Here the present author is reporting the results a successful attempt for an efficient synthesis of quinoxaline from α-bromoketones and *o*-phenylenediamine mediated by water and catalysed by SDS at room temperature in excellent yields. This is the first report of synthesizing quinoxaline derivatives in a very mild way in water catalyzed by nucleophilic SDS[121] at ambient

temperature starting from the less reactive safer precursor α-bromoketones in an efficient manner.

2. The present work

Initially, efforts were directed towards the evaluation of catalytic ability of SDS for the synthesis of quinoxalines. Preliminary studies using phenacylbromide (1 mmol) and *o*-phenylenediamine (1 mmol) without SDS in water at room temperature did not afford the desired quinoxaline. Increase of the reaction time, temperature or by changing the molar proportion of the reactants did not make any influence on the course of the reaction. Addition of some common salts like NaCl, NH_4Cl, KBr *etc.* had no positive effect on the reaction. Similar molar ratios of substrates in tap water yielded the desired product only in presence of catalytic amounts of SDS (Scheme 33). The modified method gave excellent yield of the product within 6 hours at room temperature (Scheme 33). Thus, the catalytic role of SDS in the present transformation is well established.



Scheme 33 SDS catalyzed synthesis of quinoxaline

2.1 Results and Discussion

This excellent catalyzing ability of SDS inspired us to investigate the above transformation in details. In order to evaluate an optimized and general reaction protocol, a couple of experiments were carried out (Table 1) using varying amounts of SDS (0.34 mol%, 0.17 mol%, 0.06 mol%, 0.03 mol%, 0.02 mol% and 0.01 mol%) in combination with different types (both cationic and anionic) and proportions of surfactants *viz.* tetra-n-butylammonium bromide (TBAB), cetyl trimethyl ammoniumbromide (CTAB), cetyl pyridiniumchloride (CPC), sodium dodecylbenzenesulfonate (SDBS) and tetra-n-butylammoniumiodide (TBAI), in different reaction conditions for the above model study (Table 5). It is interesting to note that, although all the surfactants can afford quinoxaline as the major product but their combination with SDS showed excellent selectivity not only in forming the desired product but also in directing the reaction to pro.ceed in a very

cleaner way (Entry 1-7, Table 1). Thus it was established that, α-bromoketone (1 mmol) and 1,2-diamine (1 mmol) in water (3 mL) gave the best result within 6 hrs in presence of SDS (10 mg, 0.03 mol%) at room temperature.

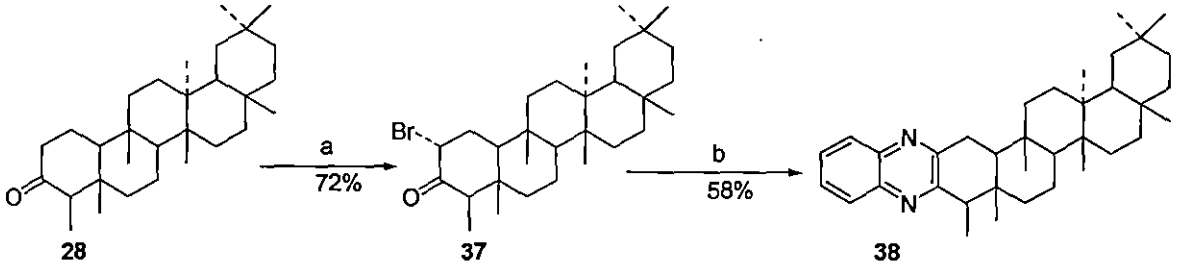
Table 5 Optimisation of quinoxaline synthesis using phenacyl bromide and *o*-phenylenediamine in presence of different surfactants and their amounts.

Entry	Ratio of aldehyde and diamine	Surfactant	Amount of surfactant (mg)	Temp (°C)	Time (hr)	% Yield[a] of 3
1	1:1	SDS	100	RT	6	96
2	1:1	SDS	50	RT	6	94
3	1:1	SDS	20	RT	6	96
4	1:1	SDS	15	RT	6	94
5	1:1	SDS	10	RT	6	95
6	1:1	SDS	7	RT	12	80
7	1:1	SDS	5	RT	15	64
8	1:1	SDS	5	50	8	68
9	1:1	TBAB	100	RT	10	78
10	1:1	TBAB	100	50	10	76
11	1:1	TBAB	200	100	10	80
12	1:1	CTAB	100	RT	10	66
13	1:1	CTAB	200	100	10	68
14	1:1	CPC	100	RT	10	78
15	1:1	CPC	200	100	10	80
16	1:1	TBAH	100	RT	10	76
17	1:1	TBAH	200	100	10	78
18	1:1	TBAI	100	RT	10	68
19	1:1	TBAI	200	100	10	74
20	1:1	SDBS	100	RT	8	82
21	1:1	SDBS	50	RT	8	80
22	1:1	SDBS	30	RT	8	64
23	1:1	SDBS	30	50	10	70

[a] % Yield refers to the isolated yield of all the compounds after chromatographic seperation.

It was also observed that during the reaction the substrates and reactants do not mix together in water; addition of SDS not only raised the solubility of the components in water but also catalyzed the process tremendously. Addition of catalytic amount of SDS (0.03 mol %) turned the reaction mixture into a clear yellowish colored solution that slowly transferred into reddish yellow as the reaction progressed. After completion of the reaction (checked by tlc), products were purified by simple filtration (and in some cases by column chromatography, silica 60-120 mesh) followed by crystallization to get the products in good to excellent yields.

Potential of pentacyclic triterenod as bioactive candidate is well described. In order to see the effect on their bioactivities by the introduction of quinoxaline ring on ring A, the present author applied the developed protocol on 2α-bromofriedelin (**37**) (prepared from friedelin) (**28**) and isolated the corresponding quinoxaline derivative (**38**) in 58% yield within 8 hours under identical condition (0.03 mol% of SDS). This is also the very first report of preparing quinoxaline derivative of pentacyclic triterenoids in water at room temperature (Scheme 34).



a, HBr, Br_2, CH_3COOH; b, Water, SDS, *o*-phenylenediamine, RT, 8h

Scheme 34 Synthesis of benzopyrazine or quinoxaline derivative of friedelin

For the synthesis of the benzopyrazine derivative of friedelin, first friedelin was isolated from cork through soxhlet apparatus (Vide infra). Friedelin was found as white powdered material of melting point 260-262 °C. In the IR spectrum it showed a characteristic peak for the presence of a six membered ketone moiety. In its ^1H NMR spectrum taken in $CDCl_3$, it showed the presence of eight methyl groups at δ_H 0.72 (s, 3H, $-CH_3$), 0.76 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$), 0.92 (s, 3H, $-CH_3$), 1.00 (s, 3H, $-CH_3$), 1.05(s, 3H, $-CH_3$), 1.18(s, 3H, $-CH_3$). All other ^1H NMR peaks are in good agreement with that reported for friedelin. In the ^{13}C NMR spectrum C-3 appeared at δ_C 213.1 (C-3) and the carbon atoms of different methyl groups appeared at δ 7.2 (C-23), 14.6 (C-24), 18.5 (C-25), 15.7 (C-26), 18.7 (C-27), 32.1 (C-28), 31.8 (C-29), 32.8 (C-30). All other peaks are in good agreement with that reported for friedelin, **28**.

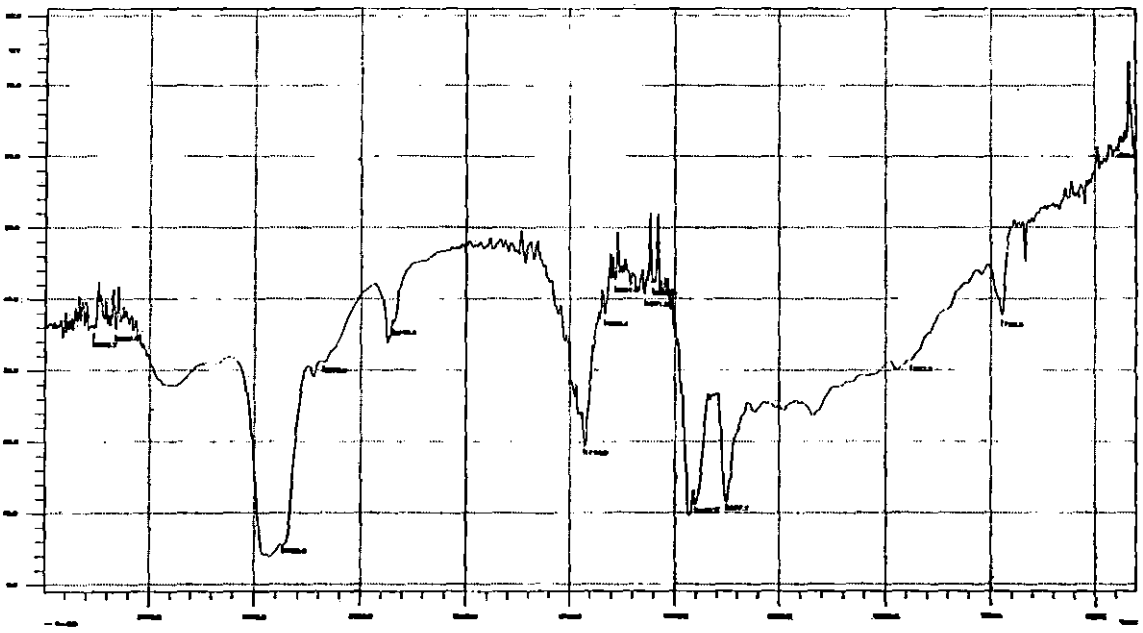


Figure 28 IR spectrum of friedelin, **28**

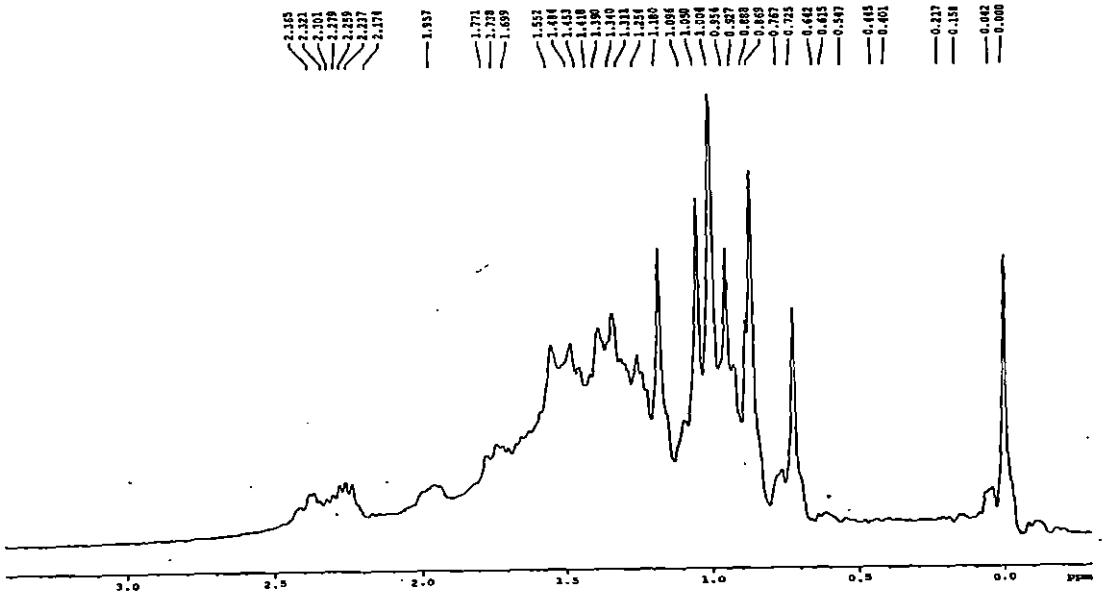
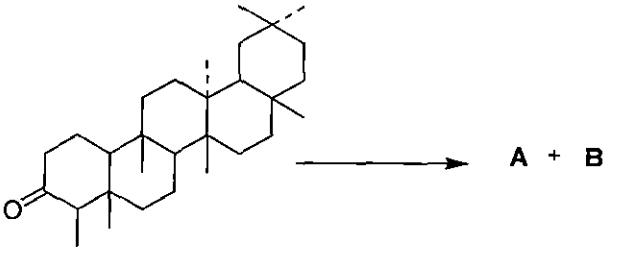


Figure 29 Expanded ^{1}H spectrum of friedelin, **28**

2α-bromofriedelin was prepared from friedelin[87] following the process of E. J.Corey and J. J. Ursprung[87] in stirring chloroform solution by adding bromine (vide infra) at room temperature in 72% yield. The reaction mixture was worked up with chloroform and

purified over a column of silica gel (60-120 mesh). It showed two distinct spots in the tlc plate, thus signifying the presence of.



28

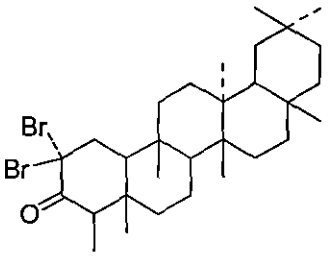
Scheme 34 Direct bromination of friedelin

2.1.1 Characterization of compound A

Compound A was purified as white powdered material of melting point 199-200 °C. In its IR spectrum it gave peaks at 1715, 1448, 1391, 916 and 787 cm^{-1}. The IR spectrum showed the presence of a six membered cyclic ketone moiety. In its mass spectrum (Figure 30) it showed molecular ion peak at m/z 584 and three distinct peaks at m/z 582, 584, 586 in a ration of 1:2:1. The appearance of such type of peaks in definite ratio indicated the presence of two bromine atoms in the molecule of A. From elemental analysis and mass spectral data the molecular formula of compound A was corroborated as $C_{30}H_{48}Br_2O$. The six degrees of unsaturation coupled with the molecular formula as obtained from the mass and elemental analysis data signified the presence of five rings and a double bond in the molecule.

In the ^1H NMR spectrum (Figure 31) taken in $CDCl_3$ taking TMS as an internal standard at ambient temperature it showed a triplet at δ_H 4.01 with an integration of one proton having coupling constant, $J_{1\alpha H, 2\alpha H} = 2.7$ Hz. This was the αH atom at C-1 of the friedelan moiety. Another triplet appeared at δ_H 3.13 with an integration of one proton having coupling constant, $J_{1\beta H, 2\alpha H} = 6.6$ Hz. This was attributed to the βH atom at C-1 of the friedelin moiety. The difference in the coupling constants for the two attached hydrogen atoms at C-1 might be due to the cis or trans orientation of the βH and αH respectively to that of the βH at C-2. Eight methyl groups each appeared as a sharp singlet at δ_H 0.72 (s, 3H, $-CH_3$), 0.76 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$), 0.92 (s, 3H, $-CH_3$),

1.00 (s, 3H, -CH_3), 1.05 (s, 3H, -CH_3) and 1.18 (s, 3H, -CH_3) satisfactory to that reported for friedelan skeleton. A multiplet centered at δ_H 1.97 was due to the presence of C-4α hydrogen atom in the ring A of the pentacyclic friedelan triterpenoid skeleton. All other peaks were in agreement to that of friedelan skeleton. From these above all data it was clear that the structure of compound A is the following 2,2-dibromo friedel-3-one, **39** . In the ^{13}C NMR spectrum (Fugure 32) C-2 was deshielded significantly and appeared at δ_C 80.6. Carbonyl group at C-3 appeared at δ_C 206.5. All other peaks were in good agreement to that of friedelan skeeton.



39

2,2-Dibromo friedel-3-one

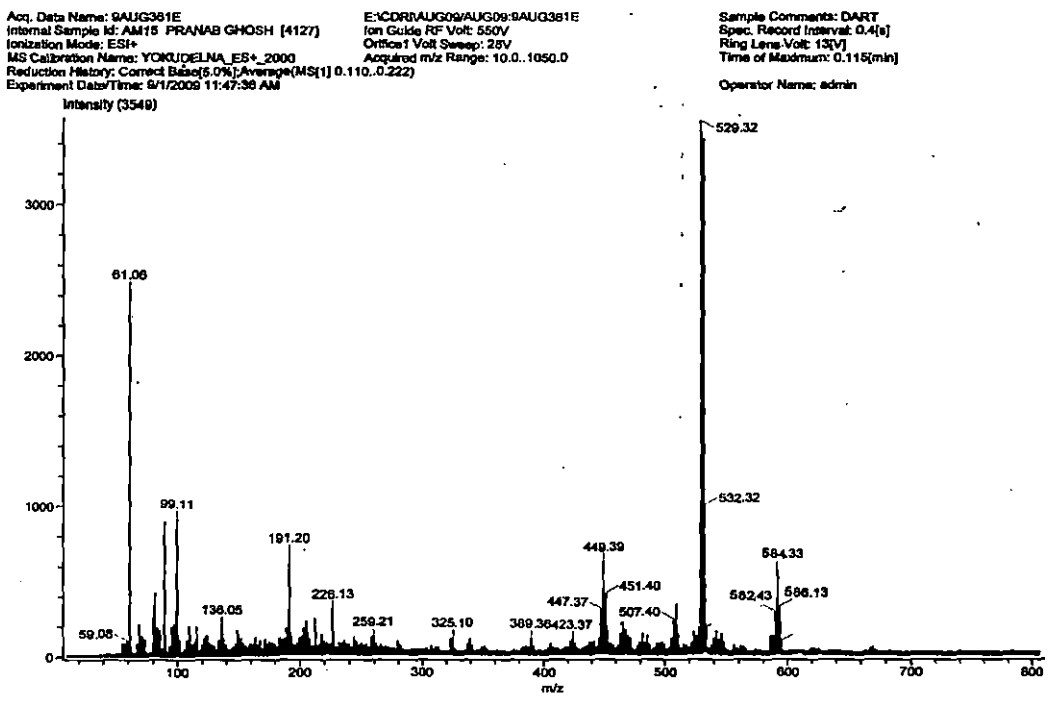


Figure 30 Mass spectrum of 2,2-dibromo friedelin, **39**

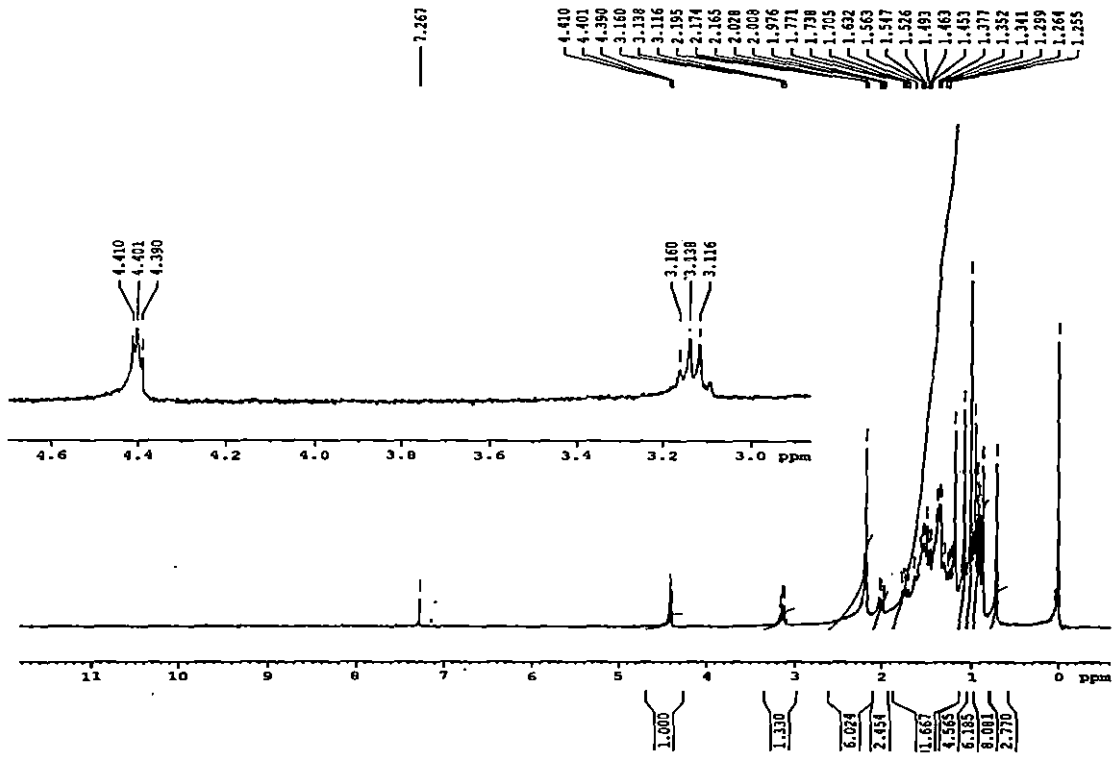


Figure 31 ^{1}H NMR spectrum of 2,2-dibromo friedelin, **39**

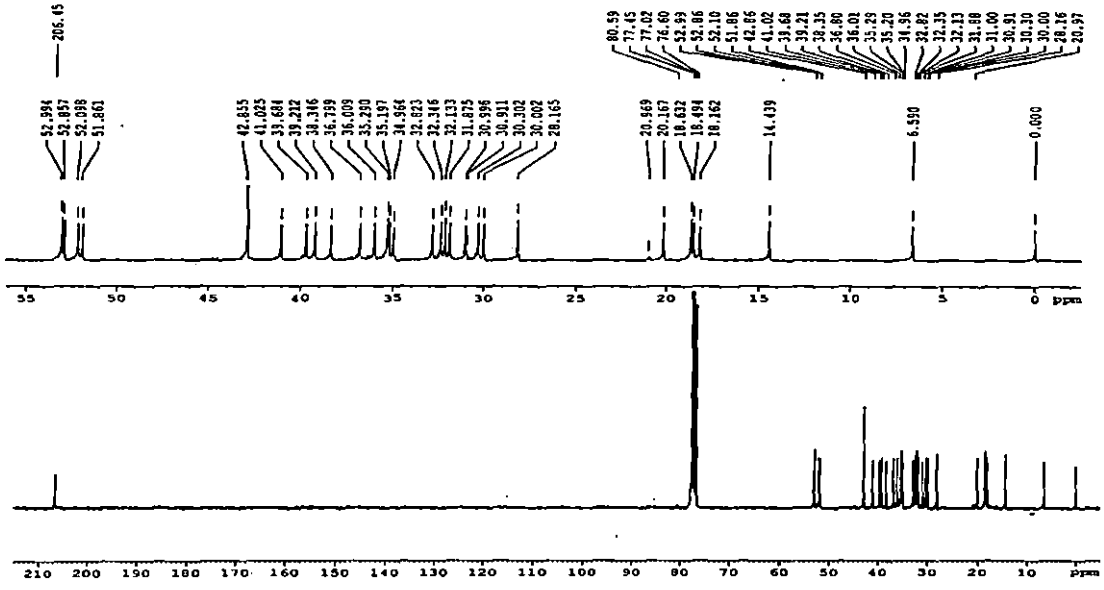


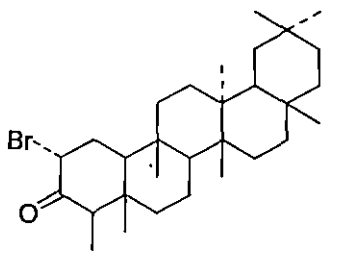
Figure 32 ^{13}C NMR spectrum of 2,2-dibromo friedelin, **39**

2.1.2 Characterization of compound B

The isolated white powdered compound, the major one, showed a melting point of 208-210 °C (the reported[87] melting point of 2α-bromofriedelin is 210 °C). Very good correlation of melting point of compound **B** to that of the reported melting point of 2α-bromofriedelin indicated that compound **B** might be the target compound. In the IR spectrum (Figure 33) it showed sharp peaks at 1715 cm^{-1} for the presence of a six membered ketone. Other peaks appeared at 2940, 2864, 1457, 1388, 1181 and 594 cm^{-1}. In the mass spectrum (Figure 34) it showed the molecular ion peak at m/z 504, another peak at m/z 506 appeared at a ratio of 1:1 to that of the molecular ion peak. The appearance of such type of peaks in the definite ratio indicated the incorporation of a single bromine atom into the triterpenoid skeleton. From the elemental analysis and the mass spectral data the molecular formula of compound **B** was assigned as $C_{30}H_{49}BrO$. Here also the six degrees of unsaturation coupled with the molecular formula as obtained from the mass and elemental analysis data signified the presence of five rings and a double bond in the molecule.

In the ^1H NMR spectrum (Figure 35, 36), it showed the presence of eight tertiary methyl groups at δ_H 0.72 (s, 3H, $-CH_3$), 0.89 (s, 3H, $-CH_3$), 0.96 (s, 3H, $-CH_3$), 1.00 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$), 1.18 (s, 3H, $-CH_3$) and 1.25 (s, 3H, $-CH_3$). A doublet of a doublet centered at δ_H 1.87 (dd, 1H, J = 2.3 and 15.2 Hz) was due to the presence of C-4α hydrogen atom in the ring A of the pentacyclic friedelan triterpenoid skeleton. Another multiplet with an integration of only one proton appeared at δ_H 3.22 (m, 1H). A large deshielding nature of the appeared proton might be attributed by the fact that it is the βH at C-2 and the observed large deshielding obviously due to the magnetic anisotropy induced by the attached electronegative brominr atom. Two hydrogen atoms at C-1 of the friedelan skeleton were also deshielded by the magnetic anisotropy induced by the bromine atom at C-2 and each appeared as a distinct multiplet at δ_H 2.94 (m, 1H, αH at C-1) and 2.71(m, 1H, βH at C-1). All other peaks are in close similarity to that of friedelan skeleton. In the ^{13}C NMR spectrum (Figure 37) C-2 appeared at δ_C 70.4 and the carbonyl carbon at C-3 appeared at δ_C 198.2. Eight methyl groups each gave a sharp singlet at δ_C 7.6 (C-23), 14.5 (C-24), 18.0 (C-25), 20.2 (C-26), 18.6 (C-27), 32.1 (C-28),

35.0 (C-29) and 31.8 (C-30). All other skeletal carbon atoms gave distinct peaks and all are in very good agreement to the for friedelan skeleton. On the basis of all these data, the structure of compound **B** was suggested as 2α-bromofriedel-3-one, **37.**



37
2a-bromofriedel-3-one

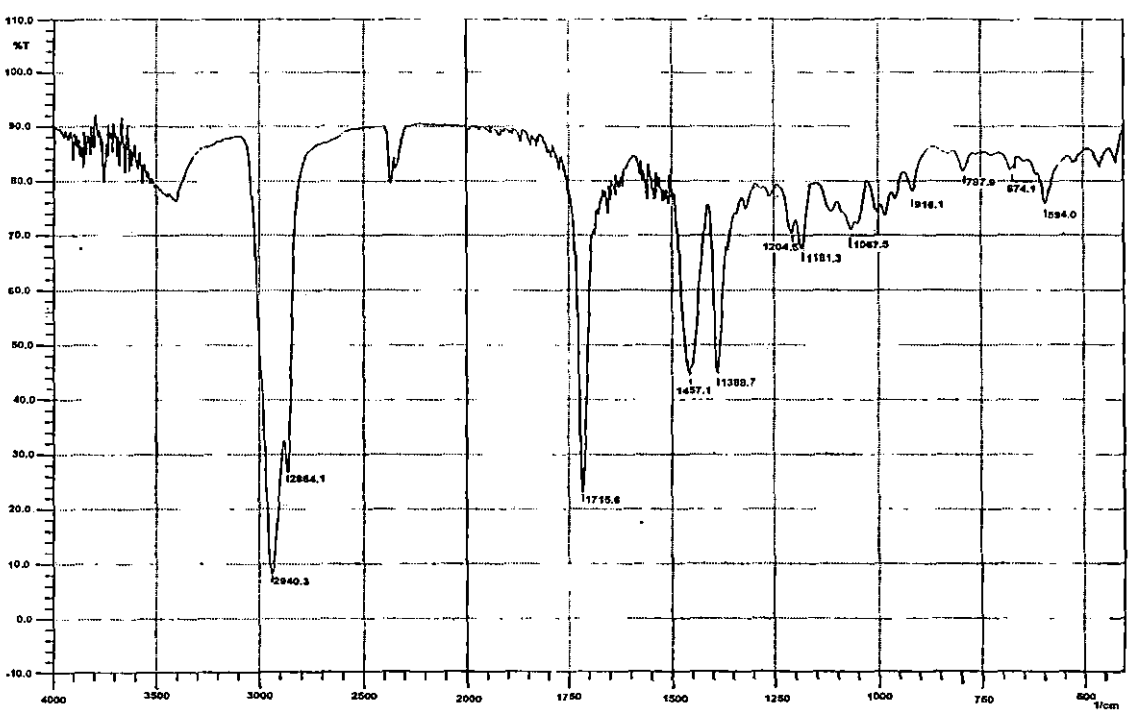


Figure 33 IR spectra of 2α-bromofriedelin, **37**

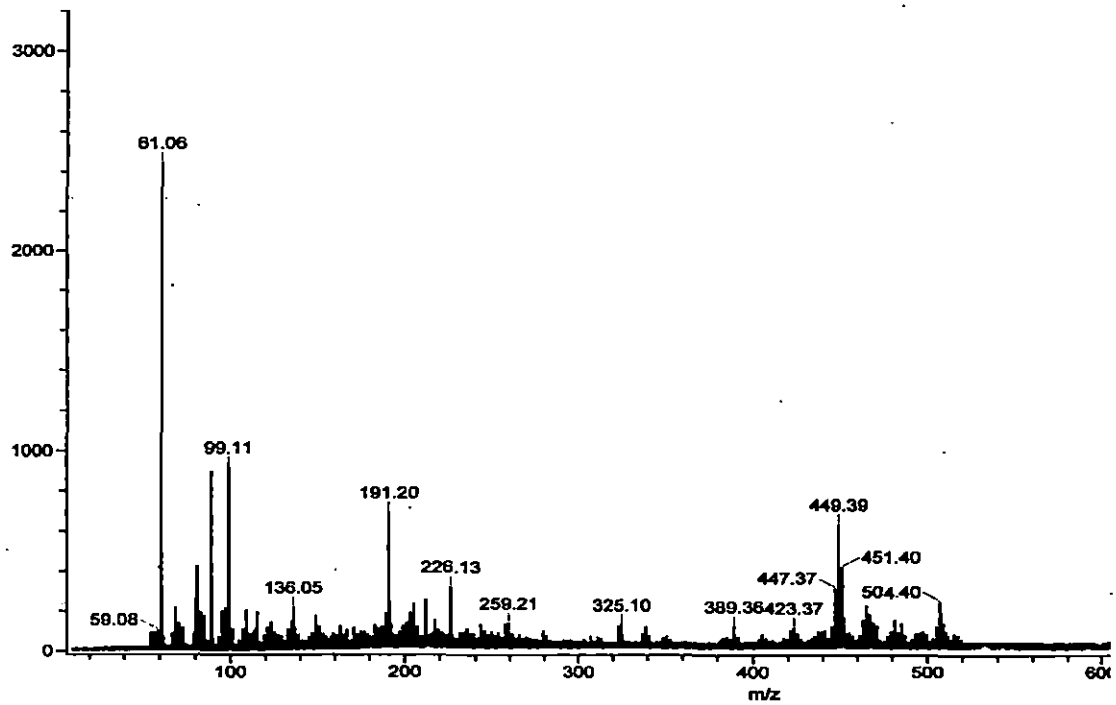


Figure 34 Mass spectrum of 2α-bromo friedelin

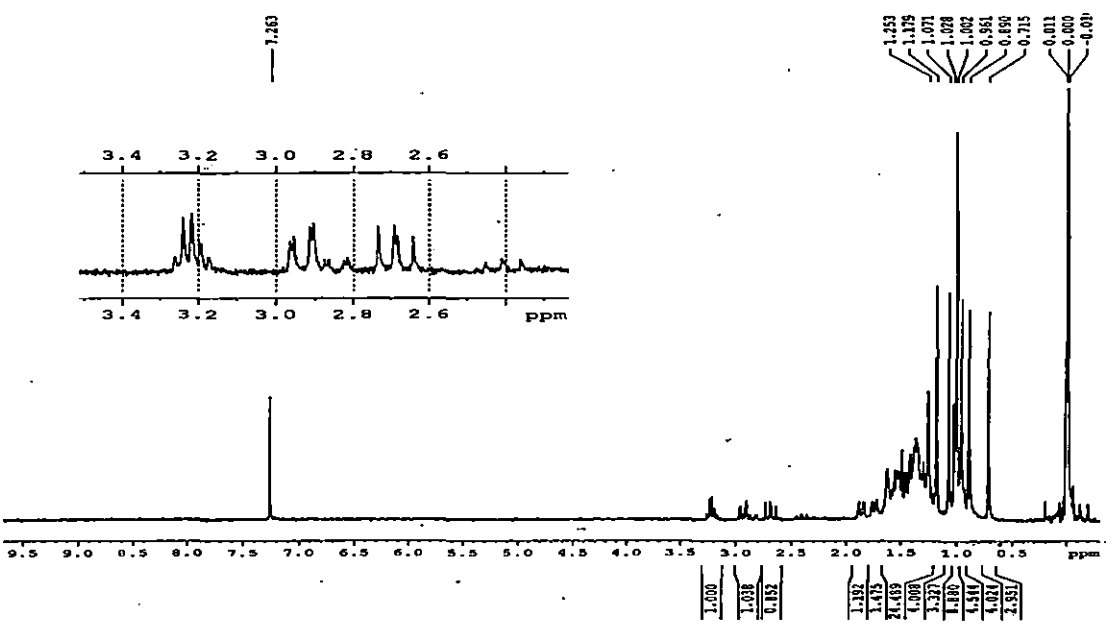


Figure 35 ^{1}H NMR spectrum of 2α-bromofriedelin

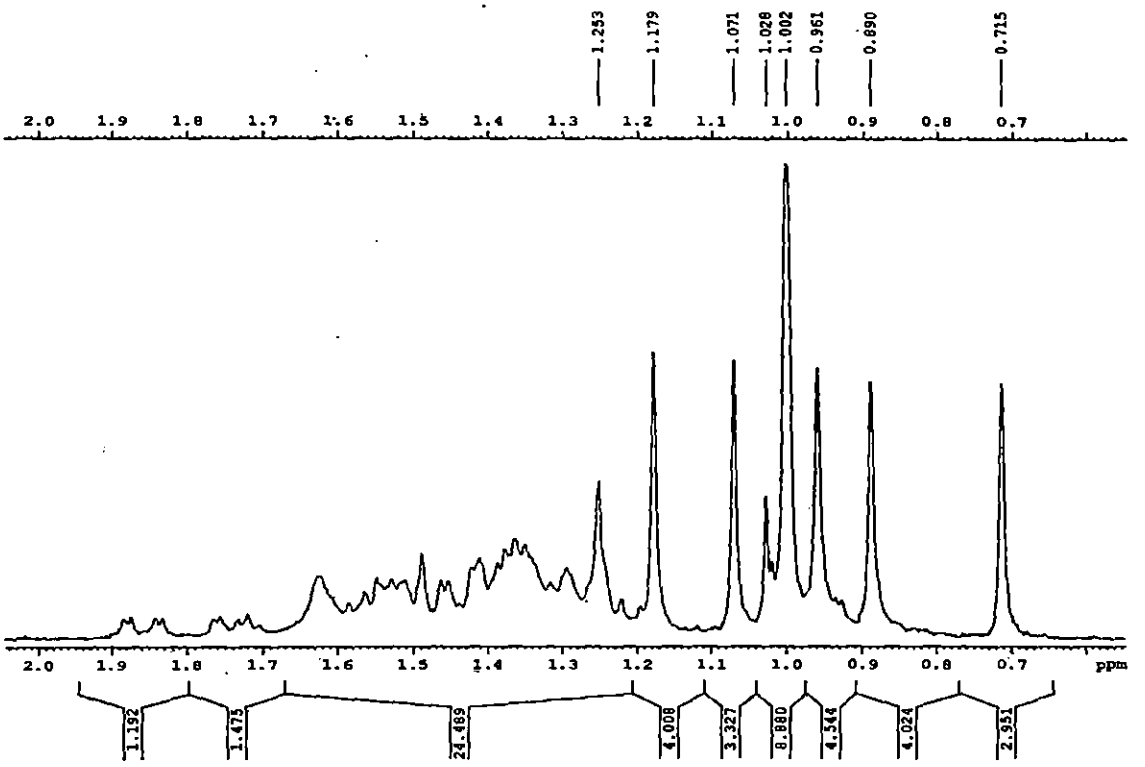


Figure 36 Expanded ^{1}H NMR spectrum of 2α-bromofriedelin

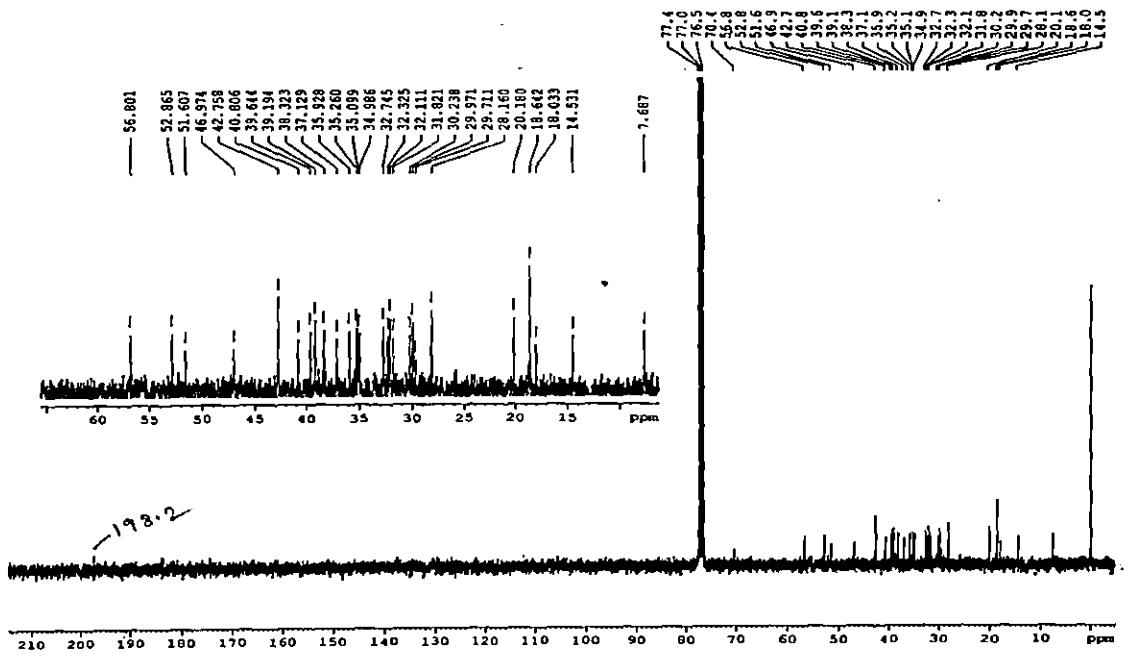


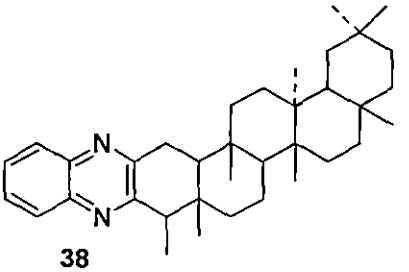
Figure 37 Expanded ^{13}C NMR spectrum of 2α-bromofriedelin

2.2 Synthesis of benzopyrazine or quinoxaline derivative of friedelin

2α-bromofriedel-3-one prepared so far was treated with *o*-phenylenediamine in tap water using SDS as the catalyst under stirring condition at room temperature. After 8 hours at the end of the reaction as revealed by tlc, the reaction mixture was worked up with ethyl acetate (Videinfra) and dried over anhydrous sodium sulfate. After drying the reaction mixture showed a single compound in tlc. It was then purified over a column of silica gel (60-120 mesh).

Purification of the reaction mixture gave a white powdered compound of melting point 248-250 °C (248-151 °C as reported).[88] In its mass spectrum it showed a molecular ion peak at m/z 512. From the elemental analysis and the mass spectral data the molecular formula of the synthesized compound should be $C_{36}H_{52}N_2$. In the IR spectrum (Figure 38) it gave peaks at 2941, 2863, 1715, 1448, 1391, 1214, 1186, 1067, 916, 787.9 and 674 cm^{-1}. It showed a molecular ion peak at m/z 512 in its mass spectrum (Figure 39), thus confirming the incorporation of quinoxaline moiety. In the ^1H NMR spectrum (Figure 40) eight methyl groups appeared as a sharp singlet at δ_H 0.72 (s, 3H, $-CH_3$), 0.76(s, 3H, $-CH_3$), 0.83(s, 3H, $-CH_3$), 0.88(s, 3H, $-CH_3$), 0.92(s, 3H, $-CH_3$), 1.00(s, 3H, $-CH_3$), 1.05(s, 3H, $-CH_3$), 1.15(s, 3H, $-CH_3$). Four aromatic hydrogen atoms appeared at δ_H 7.43 (t, 1H, J = 7.8 Hz); 7.58 (dq, 1H, J = 2.4 Hz and 8.1 Hz); 8.00 (dt, 1H, J = 2.7 Hz and 7.8 Hz); 8.09 (m, 1H). In the ^{13}C NMR spectrum (Figure 41) eight methyl groups gave singlet at δ_C 13.5 (C-23), 16.2 (C-24), 18.0 (C-25), 20.2 (C-26), 18.6 (C-27), 32.1 (C-28), 35.0 (C-29) and 31.8 (C-30). The attached heterocyclic ring structure to the ring A of the pentacyclic triterpenoid induced a deshielding effect to the methyl groups at C-4 (C-23 methyl) and at C-5 (C-24 methyl) and that is why these two methyl groups appeared in a larger deshielded position with respect to that for simple friedelan skeleton. Moreover, the extent of deshielding influence for the methyl group at C-4 (δ_C 13.5, whereas the same appeared at δ_C 7.6 in 2α-bromofriedel-3-one) is found to be larger than that for at C-5 (δ_C 16.2, whereas the same appeared at δ_C 14.5 in 2α-bromofriedel-3-one). This observed greater deshielding of the methyl group at C-4 (C-23 methyl) might be due to the fact that it is nearer to the incorporated heterocyclic moiety at ring A of the pentacyclic structure than that at C-5 (C-24 methyl). Aromatic carbon atoms appeared at δ_C 128.3, 129.8, 130.3, 131.0, 133.8, 134.7, 168.3 and 170.6. All the above spectral and

physical data can be explained by considering the following structure to the synthesized compound.



38

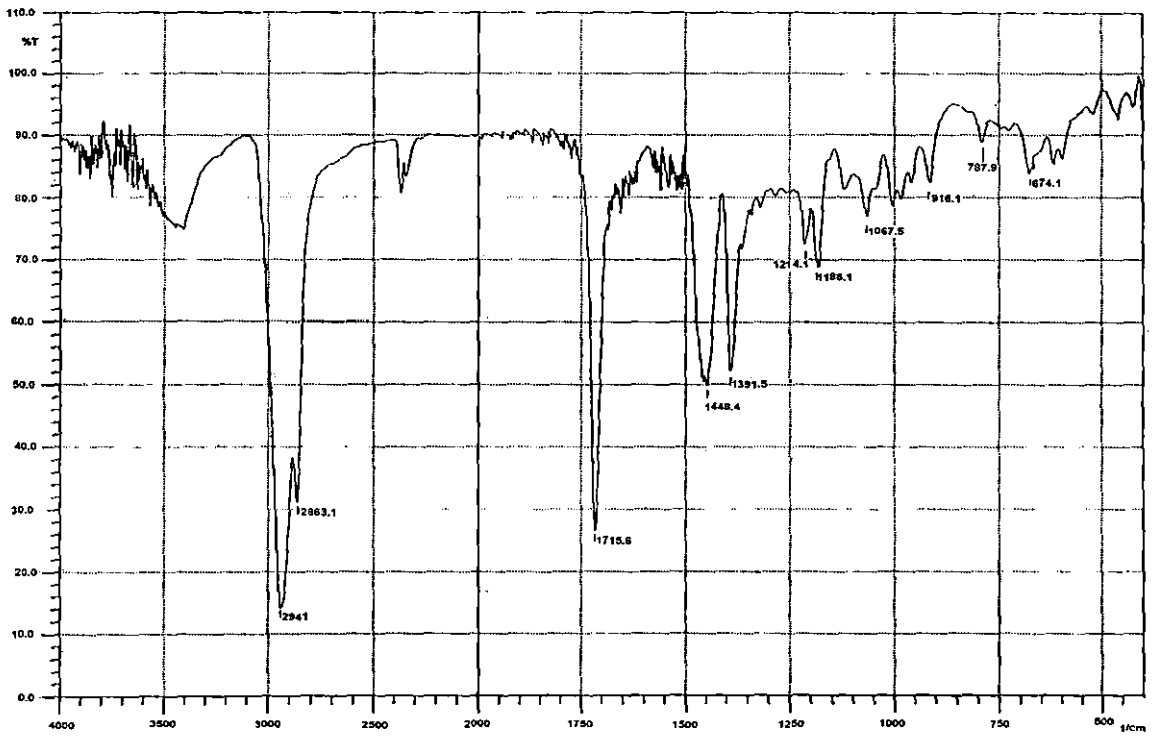


Figure 38 IR spectrum of friedelin quinoxaline derivative, **38**

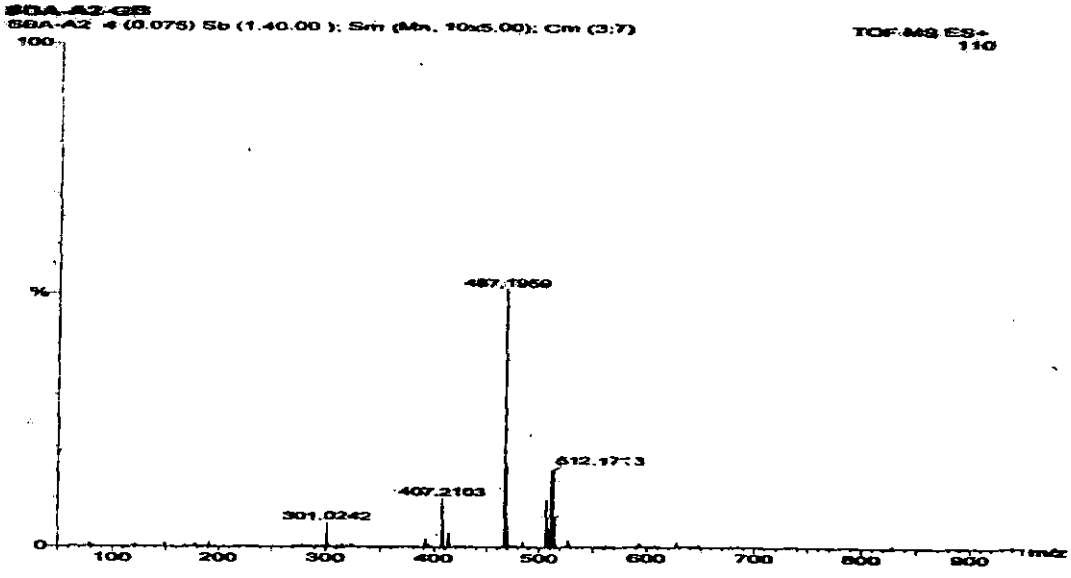


Figure 39 Mass spectrum of the quinoxaline derivative of friedelin, **38**

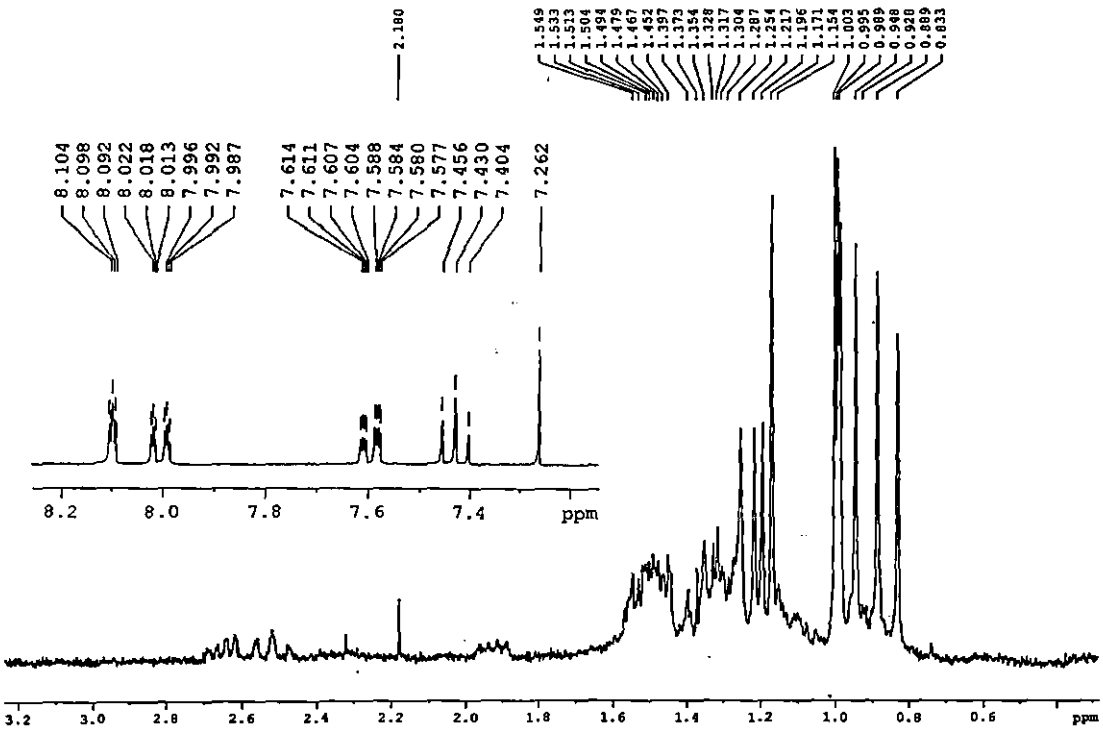


Figure 40 ^{1}H NMR spectrum of benzopyrazine derivative of quinoxaline, **38**

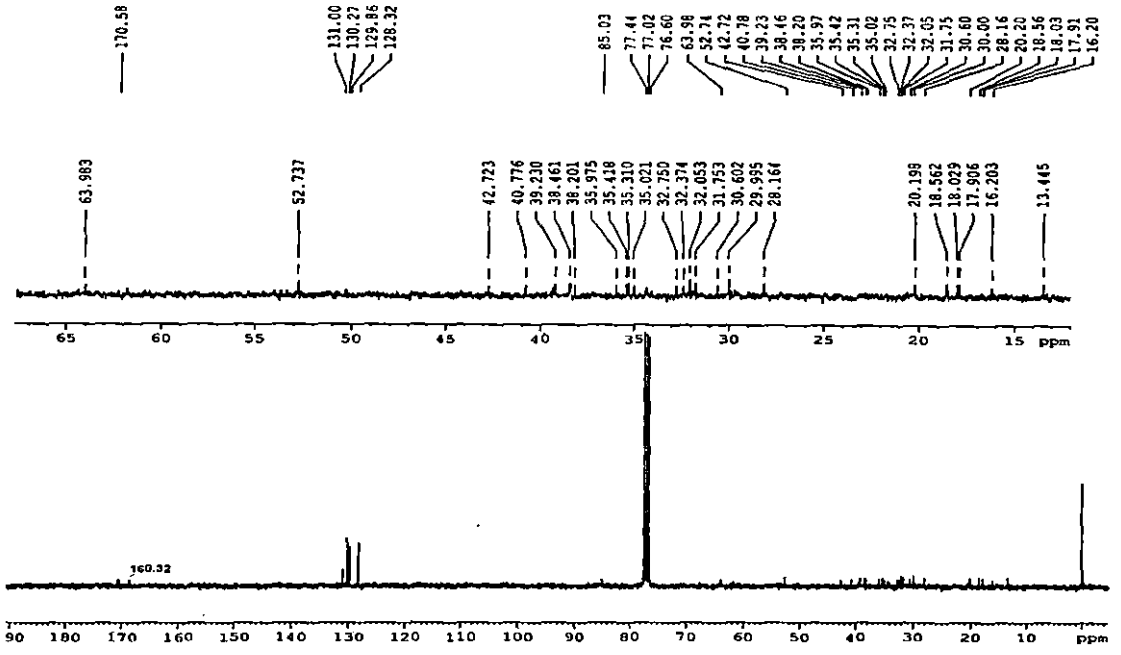


Figure 41 ^{13}C NMR spectrum of friedelin quinoxaline derivative, **38**

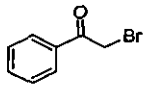
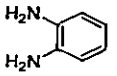
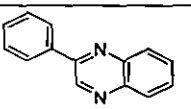
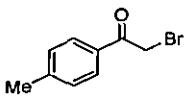
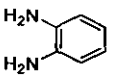
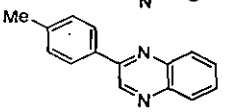
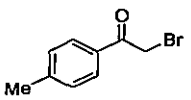
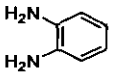
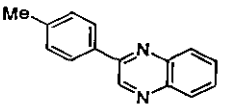
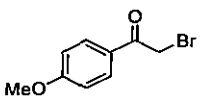
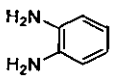
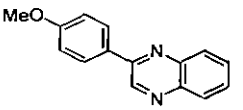
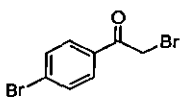
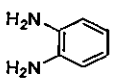
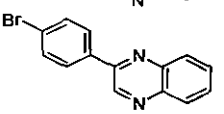
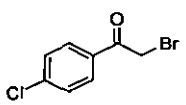
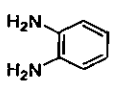
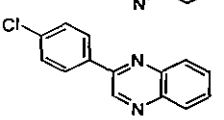
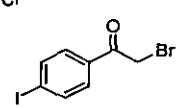
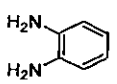
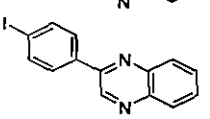
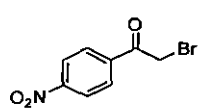
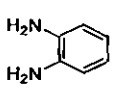
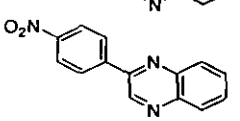
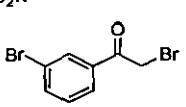
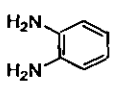
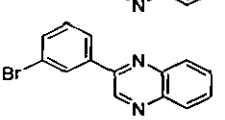
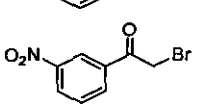
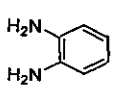
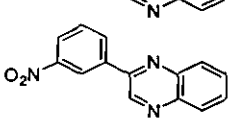
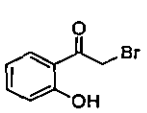
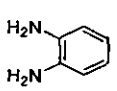
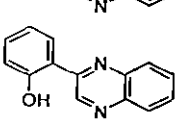
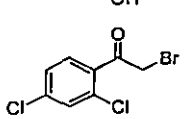
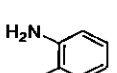
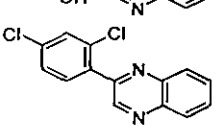
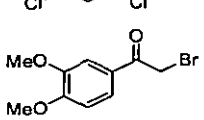
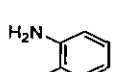
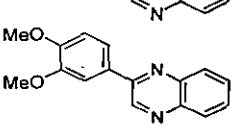
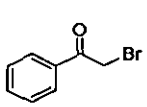
Unfortunately similar transformatiom with the 2,2-dibromo friedelin did not yield the desired product under the same reaction condition.

2.3 Versatility of the developed protocol

In order to demonstrate the versatility of SDS as a catalyst for the synthesis of quinoxalines, a series of α-bromoketones and 1,2-diamines were subjected to undergo one pot condensation-aromatization in presence of SDS under the optimized reaction protocol (Table 6). All of the reactions tried showed good selectivity with excellent isolated yields. While investigating the influence of the substituents present either on ketone part or on 1,2-diamine on the course of the reaction, it was observed that compounds having electron donating or withdrawing groups on the ketone (Entry 2, 3, 5, 6, 7 and 8, 9, of Table 6) both underwent the reactions in almost similar fashion and gave good yields. Although, *p*-bromo phenacylbromide (Entry 5, of Table 6) gave better yield than its meta isomer (Entry 9, of Table 6), the corresponding *p*-nitro and *m*-nitro derivative underwent the reaction in identical fashion (Entry 10, of Table 6). Disubstituted α-bromoketones (Entry 11, 12, of Table 6) also gave excellent yields of the

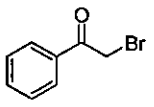
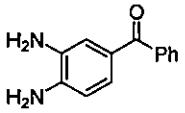
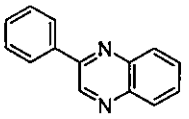
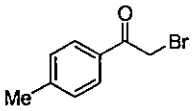
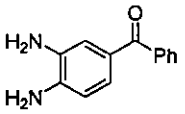
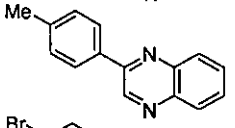
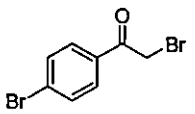
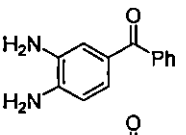
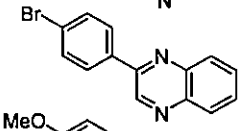
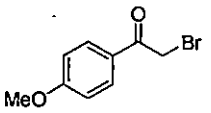
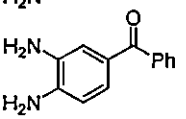
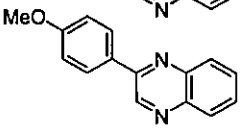
expected quinoxalines. Sensitive molecules like 1,2-diaminomalionitrile (Entry 15, of Table 6) was also found compatible to the reaction condition and gave 84% yield of the corresponding quinoxaline. All the observed results were summarized in table 6.

Table 6 Preperation of quinoxaline derivatives.

Entry	α-Bromo carbonyl compound	Diamine	Time (h)	Product	%Yield
1			6		94
2			6		92
3			6		92
4			6		86
5			6		92
6			6		89
7			6		87
8			7		84
9			6		87
10			8		85
11			7		83
12			6.5		98
13			7		82
14			6		92
15			5		84

% Yield refers to the isolated yield of all the compounds.

Continuation of **Table 6**

Entry	α-Bromo carbonyl compound	Diamine	Time (h)	Product	%Yield
16			6.5		88
17			6		86
18			6		86
19			6		86

% Yield refers to the isolated yield of all the compounds.

2.3 Proposed mechanism for the present transformation

It is well known that under ambient condition surfactant molecules can aggregate in an aqueous phase to micelles with hydrophobic core and a hydrophilic corona.[122,123] To determine whether micellisation had occurred or not we first measured the CMC (critical micellisation concentration) of SDS (Figure 42) and the value was found to be 8.33 mM. In the present study, under the optimized reaction condition the concentration of SDS was 11.57 mM (10 mg of SDS in 3 ml water). Since the value was far beyond the CMC value of SDS (8.33 mM), micellization was anticipated.

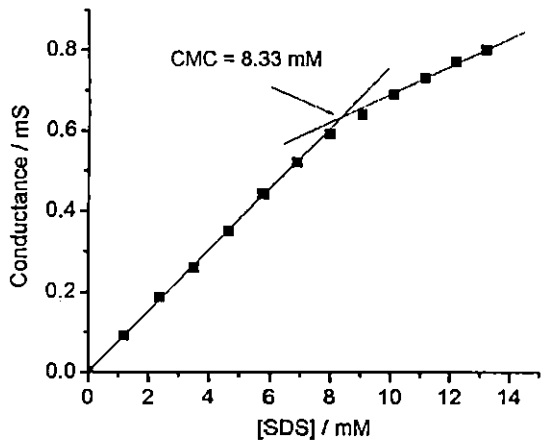


Figure 42 Plot of conductance vs. concentration of SDS for the calculation of CMC value of SDS

It was reported in the literature[124] that the dimensionless packing parameter P of the molecular geometry as an index to predict the size and shape of the micelles. P was defined as $V/(a_0 l)$, where V is the hydrocarbon chain volume, a_0 is the optimum head group area per molecule, and l is the hydrocarbon chain length that is taken to be ca. 80-90% of the fully extended chain length.[124] The overall prediction was concluded as follows:

Spherical micelles $P < 1/3$

Cylindrical micelles $1/3 < P < 1/2$

Bilayers (or vesicles) $1/2 < P < 1$

Inverted structures $P > 1$

The value of packing parameter P, an index to predict the size and shape of the micelles,[124] of SDS was found to be 0.235 (taking l as 90 % of the fully extended chain length) indicating the spherical nature of the developed micelles.

For further confirmation DLS (Dynamic Light Scattering) measurement was carried out of a 11.57 mM aqueous solution of SDS that indicated the presence of micelles (Figure 43) of radius 161 nm (diameter of 322 nm) with the PDI (Polydispersity index) of 0.348.

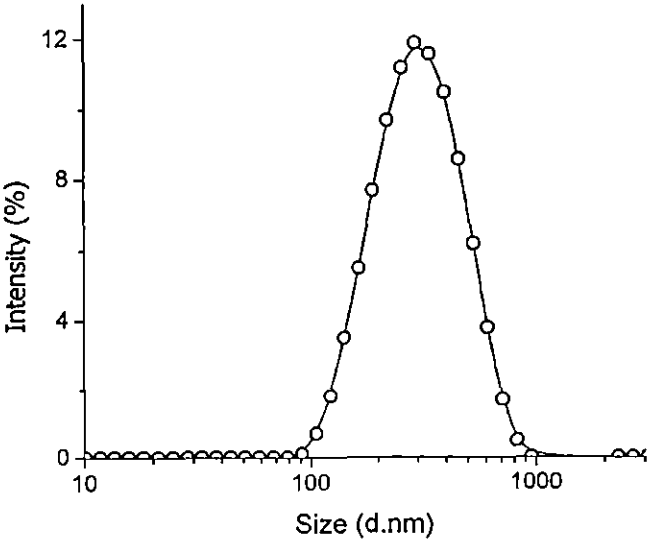


Figure 43 Graph of intensity vs. size (nm) of the micelles based on DLS measurement.

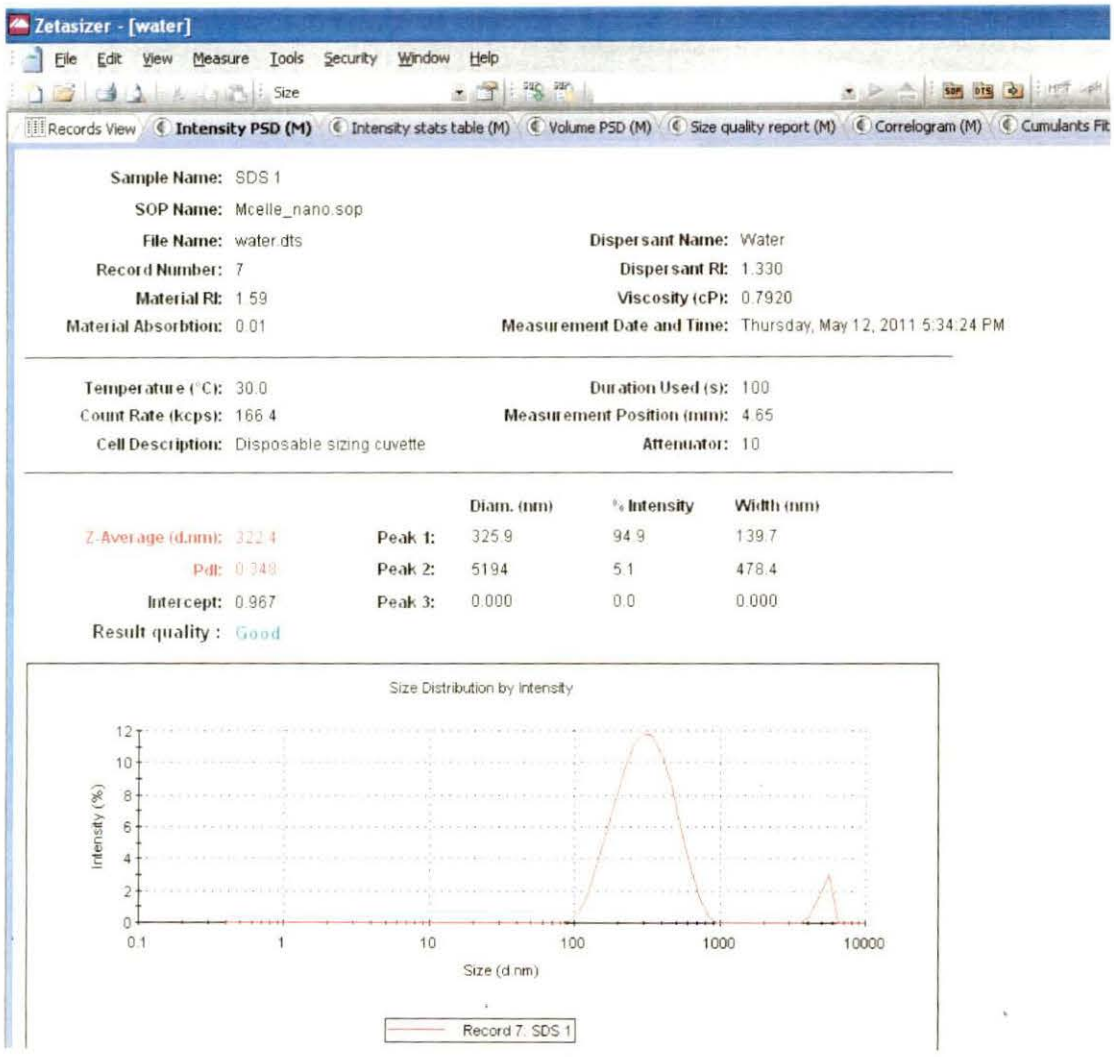
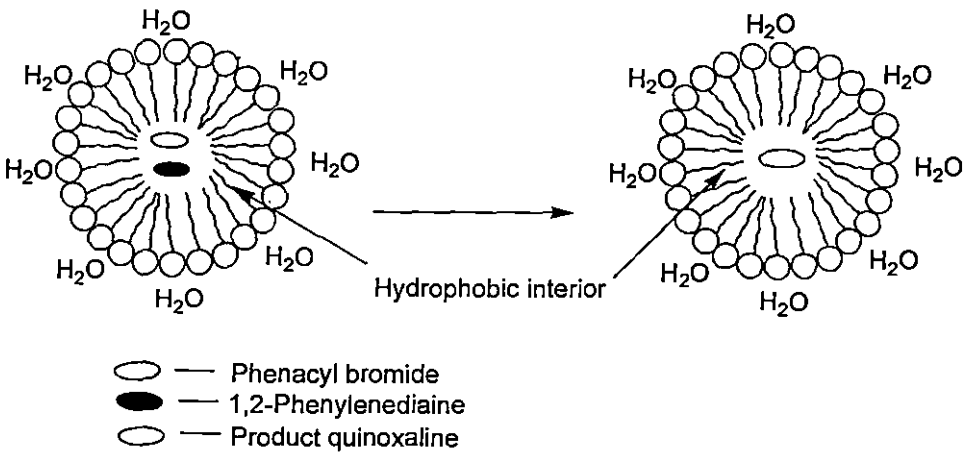
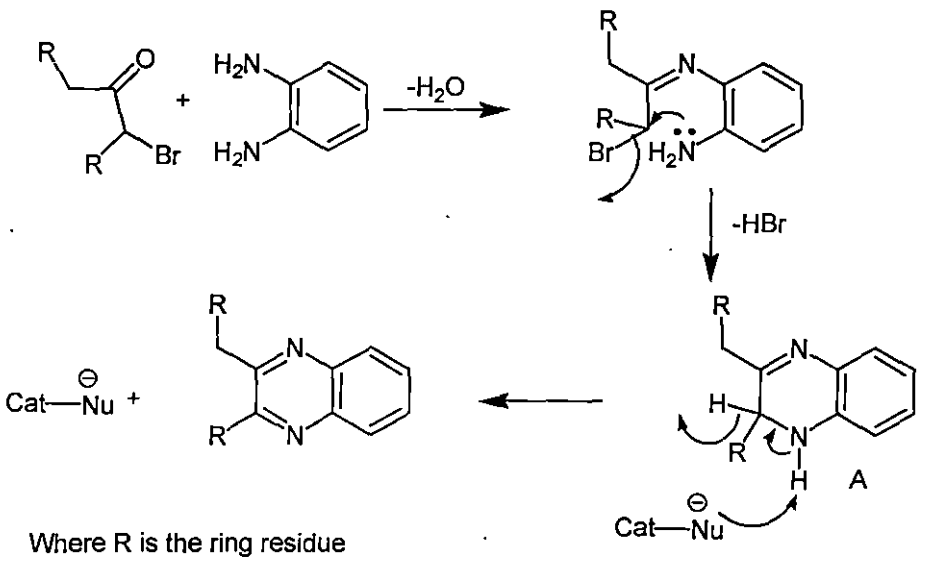


Figure 44 Machine characterization of the formation of the spherical micelle of radius 161 nm.

The role of SDS as a nucleophile is well investigated in literature.[121] Considering the above caharacteristics of SDS, the most probable mechanism of the miceller SDS in effecting the present transformation may be depicted as shown in scheme 35. In the miceller solution, 1,2-phenylenediamine and phenacyl bromide, both of which are hydrophobic in nature, are entered into the hydrophobic core of the micelles and thus assist the condensation between the phenacyl bromide and *o*-phenylenediamine to form dihydroquinoxaline derivative, **A** (Scheme 35 and 36). Nucleophilic nature of SDS may have assisted the in situ aromatization of the dihydro derivative (**A**) to afford quinoxalines (Scheme 36).



Scheme 35 Proposed model for the synthesis of quinoxaline in water-SDS



Scheme 36 Plausible mechanism of the SDS catalysed quinoxaline formation.

2.4 Recyclability of the catalyst

As was mentioned earlier, a simple filtration or easy work up procedure of the reaction and reuse of the catalyst, SDS directly from the aqueous extract of the reaction mixture for a fresh run, are the great advantages of the developed process. Gratifyingly, it was tested that the recovered water layer can be reused for six consecutive runs (Table 7).

Table 7 Recycling experiment using SDS

Entry	No. of Cycle	% Yield
1	0	92
2	1	87
3	2	82
4	3	78
5	4	72
6	5	68

% Yield refers to the isolated yield of the c ompound afterchromatography.

3. Conclusion

A simple, energy efficient, one step SDS catalyzed (0.03 mol%) greener method for the synthesis of benzopyrazines or quinoxaline derivatives under water mediating condition has been developed. Structurally diversified α-bromoketones, commonly regarded as safer chemicals, were used as reaction partners of 1,2-diamines in water at ambient temperature. Effect of the nature and position of the substituents on both the reactants in consideration to the reaction condition was also studied. Disubstituted α-bromoketones and 2α-bromo friedelin (a representative of pentacyclic triterpenoids) also formed the corresponding quinoxalines that may serve as lead compound in near future. Except water, no other organic solvents were used. The ambient reaction conditions, comparatively lower reaction time, excellent product yields and simple work up procedure not only make this methodology an alternative platform to the conventional acid/base catalyzed thermal processes, but also found to be significant under the umbrella of environmentally greener and safer processes that may find its place in industry. Moreover, water as a solvent used with miceller SDS has both economic and environmental advantages. As micelles of diameter of 322 nm (radius 161 nm) were formed, it was anticipated that the entitled reactions were occurring inside the hydrophilic core of the micelles. Scaling up the reaction upto 5 moles scale gave good results. We believe our developed process not only satisfied the principles of green chemistry, can open a new way of synthesizing bioactive molecules by catalyzing SDS in water.