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Synthesis of Indolo-benzodiazocine Derivatives in Aqueous Micellar Medium and their Anthelmintic Activity

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Abstract: An efficient, facile and environmentally benign synthesis of 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4]benzodiazocine was carried out by the reaction of 3-(2-oxo-2-(2-thienyl)ethylidene)indol-2-ones with *o*-phenylenediamines using tetrabutylammonium bromide (TBAB) as a surfactant under aqueous micellar medium. An analogous reaction with ethylenediamine resulted in the formation of Schiff's base derivatives, 1,3-dihydro-3-[2-(2-aminoethylimino)2-(2-thienyl)ethylidene]indol-2-ones. Synthesized compounds were characterized with analytical and spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) studies. This methodology has advantage of mild reaction conditions, high yields of products, lesser time as well as environmentally benign. All synthesized compounds were screened for anthelmintic activity against *Pheretima Posthuma.*

Keywords: 6-(2-Thienyl)-12*H*-indolo[2,3-e][1,4]benzodiazocine, 3-[(*E*)-2-(2-aminoethylimino) -2-(2-thienyl)ethylidene]indol-2-one, tetrabutylammonium bromide (TBAB), water, anthelmintic activity.

INTRODUCTION:

In recent years, one of the challenges faced by chemists is to develop new transformations that are not only efficient, selective and high yielding but also environmentally as well as economically benign. During the last decade, the topic of 'green chemistry' has received increasing attention which aims in the development of cleaner and more benign chemical processes by replacement of volatile and hazardous reagents and solvents with environmentally benign materials and thus increase the process selectivity [1-3]. In this regard, use of water in organic synthesis is both environmentally and economically benign because of the cheap, non-inflammable, non-toxic, safe and unique physical and chemical properties, easy separation of product led us to select water as a solvent [4]. Recently, surfactants have attracted considerable interest in organic synthesis because of their high catalytic activity as well

as benign character [5]. The use of surfactants in aqueous medium increase reactivity via the formation of micelles [6,7].

The indole nucleus has received wide attention of biochemists because of its significant therapeutic and biochemical properties. In this class indole-2,3-diones (Isatins) are an important group of heterocyclic compounds which are biologically active with significant importance in medicinal chemistry [8]. A literature survey shows several isatin derivatives in the development phase as potential new drugs [9]. A variety of biological activities [10-12] associated with isatins including CNS activities [13], analgesic [14], anticonvulsant [15], antidepressant [15], anti-inflammatory [16], antimicrobial [17], antitubercular [18], anti HIV [11], anticancer [19], etc.

Besides indoles, cyclic molecules with benzofused ring system play an important role in both drug discovery and chemical biology. In particular eight-membered heterocycles containing two nitrogens such as diazocines are known to exhibit a number of important biological properties such as antihypertensive, herbicidal, anti-depressant, analgesic, antitussive and anthelmintic activities [20]. Some of the [1,4] diazocino indole derivatives are used as antipsychotic and antiobesity agents [21].

Earlier, some benzodiazocine derivatives were prepared by the reaction of chalcones with *o*-phenylenediamines using different methodology [21,22]. However, in these reported methods, most of the synthetic approaches are associated with harsh reaction conditions, using environmentally black-listed solvents, prolonged reaction time and tedious isolation procedure with poor yields.

Hitherto, taking into august consideration the significance of indoles , diazocines and in continuation of our search for better and improved bioactive heterocycles [23-29], with significance of surfactants, and in the steady direction of our ongoing efforts to develop new efficient protocol for the synthesis of bioactive heterocycles employing green tools from readily available building blocks, we herein report for the first time, a green, efficient and new procedure for the synthesis of 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4] benzodiazocine **4** by the reaction of 3-[2-oxo-2-(2-thienyl)ethylidene]indol-2-ones **1** [28] with *o*-phenylenediamines in water in the presence of tetrabutylammonium bromide as surfactant with excellent yield. The Schiff's bases 3-[(*E*)-2-(2-aminoethylimino) -2-(2-thienyl) ethylidene] indol-2-one **7** were obtained by the reacting **1** with ethylenediamine, TBAB in water. It is assumed that the incorporation of more than one bioactive heterocyclic moiety into a single framework may result into the construction of heterocycles with improved bioactivity therefore all synthesized compounds were evaluated for anthelmintic activity.

Reaction of indole-2,3-dione and 2-acetylthiophene gives 3-hydroxy-3-(2-oxo-2-(2-thienyl)ethyl)indol-2-ones which on reaction with glacial acetic acid and HCl gave 3-(2-oxo-2-(2-thienyl)ethylidene)indol-2-ones **1** [28]. Investigation of reaction of **1** with *o*-phenylenediamines led to the formation of **4**, an eight membered condensed novel heterocyclic compounds *i.e.* 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4]benzodiazocine **4** instead of the expected formation of compounds **2** and **3** on account of availability of different reaction sites in the key intermediate **1**. While the analogous reaction with ethylenediamine resulted in exclusive formation of Schiff's base derivatives viz. 3-[(*E*)-2-(2-aminoethylimino)-2-(2-thienyl)ethylidene]indo l-2-one **7** in place of products **5** and **6** (**Scheme 1**).

MATERIALS AND METHODS:

Chemistry

Melting points were determined in open end capillaries using Gallenkamp melting point apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using pet.-ether and ethyl acetate (4:1) as eluent and spots were located by iodine vapours. The IR spectra were recorded on an 8400S SHIMADZU IR spectrometer using KBr pellets and band positions were recorded in wave numbers (cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as an internal reference on a JEOL spectrometer at 300 and 75MHz, respectively. The Mass spectra were recorded on XEVO G2S QTOF-YDA220 mass spectrometer. The elemental analyses were performed at Central Drug Research Institute, Lucknow, India. Chemicals were purchased from *Acros Organics*.

General procedure for synthesis of 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4] benzodiazocine (4a-g)

To a mixture of 3-(2-oxo-2-(2-thienyl) ethylidene)indol-2-one (**1a,** 0.01 mol) and *o*-phenylenediamine (0.01 mol) in distilled water (5.0 ml) , was added TBAB (0.0483g, 15 mol %). This reaction mixture was allowed to stir magnetically at 60 ˚C. Progress of the reaction was monitored by TLC (pet.-ether, ethyl acetate = 4:1) and visualization was accomplished in iodine chamber. After completion of the reaction, the solid obtained was collected by filtration and washed with warm water. The crude product so obtained was purified by crystallization with ethanol to afford pure products, **4a-g**. All the synthesized compounds were well characterized by spectral and elemental analysis.

6-(2-Thienyl)-12H-indolo[2,3-e][1,4] benzodiazocine (4a).

Yield: 91%; mp 125˚C; IR (KBr, cm^{-1}): 3180 (NH), 3000-2910 (C-H), 1620 and 1580 (C=N), 1560-1450 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 5.46 (s, 1H, C=CH), 6.41-8.30 (m, 12H, Ar-H), 9.20 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$, δ ppm): 116.13, 116.41, 118.25, 120.34, 122.40, 125.20, 128.10, 129.18, 129.49, 129.57, 129.61, 129.63, 135.37, 137.41, 139.20, 141.55, 142.25, 142.97 (Ar-C), 156.0 (C=N), 160.6 (C=N); MS: Calcd. for $C_{20}H_{13}N_3S$: 327.0830. Found: 327.0835. Anal. Calcd for $C_{20}H_{13}N_3S$: C, 73.37; H, 4.00; N, 12.83; S, 9.79%. Found: C, 73.40; H, 4.02; N, 12.80; S, 9.81%.

12-Methyl-6-(2-thienyl)-12H-indolo[2,3-e][1,4]benzodiazocine (4b).

Yield: 88%; mp 140 ˚C; IR (KBr, cm^{-1}): 3050-2990 (Ar-H), 1580, 1540 (C=N), 1510- 1475 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.25 (s, 3H, NCH_3), 5.50 (s, 1H, C=CH), 6.86-8.25 (m, 11H, Ar-H); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 35.4 (NCH_3), 116.14, 116.43, 118.26, 120.35, 122.40, 125.20, 128.12, 129.19, 129.50, 130.01, 130.05, 130.63, 135.37, 137.43, 139.22, 141.56, 142.26, 142.97 (Ar-C), 158 (C=N), 162.40 (C=N),; MS: Calcd. For $C_{21}H_{15}N_3S$: 341.0987. Found: 341.0980. Anal. Calcd for $C_{21}H_{15}N_3S$; C, 73.87; H, 4.43; N, 12.31; S, 9.39%. Found: C, 73.90; H, 4.46; N, 12.35; S, 9.37%.

9-Fluoro-6-(2-thienyl)-12H-indolo[2,3-e][1,4] benzodiazocine (4c).

Yield : 90%; mp 152˚C; IR (KBr, cm^{-1}): 3040-2960 (Ar-H), 1620 (C=N), 1580 (C=N), 1550, 1470 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 5.40 (s, 1H, C=CH), 6.58-8.20 (m, 11H, Ar-H), 9.25 (s, 1H, NH); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 116.12, 116.43, 118.26, 120.35, 122.42, 125.23, 128.12, 129.19, 129.50, 129.59, 129.62, 129.65, 135.38, 137.42, 139.21, 141.56, 142.26, 142.98 (Ar-C), 156.40 (C=N), 160.80 (C=N); MS: Calcd. For $C_{20}H_{12}FN_3S$: 345.0736. Found: 345.0730. Anal. Calcd for $C_{20}H_{12}FN_3S$; C, 69.55; H, 3.50; N, 12.17; S, 9.26%. Found: C, 69.51; H, 3.48; N, 12.19; S, 9.30%.

9-Chloro-6-(2-thienyl)-12H-indolo[2,3-e][1,4] benzodiazocine (4d).

Yield: 88%; mp 118 ˚C; IR (KBr, cm^{-1}): 3030-2970 (Ar-H), 1610 (C=N), 1580 (C=N), 1560, 1480 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 5.48 (s, 1H, C=CH), 6.45-8.15 (m, 11H, Ar-H), 9.10 (s, 1H, NH); ^{13}C-NMR(75MHz, $CDCl_3$, δ ppm): 116.14, 116.45, 118.27, 120.36, 122.44, 125.25, 128.14, 129.21, 129.52, 129.60, 129.64, 129.66, 135.39, 137.45, 139.23, 141.57, 142.28, 142.99 (Ar-C), 158.20 (C=N), 162.40 (C=N); MS: Calcd. For $C_{20}H_{12}ClN_3S$: 361.0440. Found: 361.0444. Anal. Calcd for $C_{20}H_{12}ClN_3S$; C, 66.39; H, 3.34; N, 11.61; S, 8.86%. Found: C, 66.41; H, 3.31; N, 11.59; S, 8.89%.

3-Methyl-6-(2-thienyl)-12H-indolo[2,3-e][1,4] benzodiazocine (4e).

Yield: 89%; mp 172 ˚C; IR (KBr, cm^{-1}): 3030-2980 (Ar-H), 1620 (C=N), 1590 (C=N), 1550, 1460 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 2.43 (s, 3H, CH_3), 5.46 (s, 1H, C=CH), 6.50-8.08 (m, 11H, Ar-H), 9.25 (s, 1H, NH); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 21.43 (CH_3), 116.15, 116.47, 118.29, 120.38, 122.46, 125.26, 128.16, 129.23, 129.54, 129.62, 129.66, 129.67, 135.40, 137.47, 139.25, 141.58, 142.29, 143.00 (Ar-C), 159.0 (C=N), 162.80 (C=N), ; MS: Calcd. For $C_{21}H_{15}N_3S$: 341.0987. Found: 341.0982. Anal. Calcd for $C_{21}H_{15}N_3S$; C, 73.87; H, 4.43; N, 12.31; S, 9.39%. Found: C, 73.85; H, 4.46; N, 12.35; S, 9.42%.

9-Fluoro-12-methyl-6-(2-thienyl)-12H-indolo[2,3-e][1,4]benzodiazocine (4f).

Yield: 88%; mp 136˚C; IR (KBr, cm^{-1}): 3060-2980 (Ar-H), 1610 (C=N), 1580 (C=N), 1560, 1470 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.46 (s, 3H, NCH_3), 5.39 (s, 1H, C=CH), 6.48-8.06 (m, 11H, Ar-H); ^{13}C-NMR(75MHz, $CDCl_3$, δ ppm): 35.60 (NCH_3), 116.16, 116.48, 118.27, 120.37, 122.45, 125.27, 128.17, 129.24, 129.55, 129.63, 129.67, 130.00, 135.42, 137.48, 139.27, 141.59, 142.31, 143.02 (Ar-C), 157.0 (C=N), 161.80 (C=N); MS: Calcd. For $C_{21}H_{14}FN_3S$: 359.0892. Found: 359.0888. Anal. Calcd for $C_{21}H_{14}FN_3S$; C, 70.18; H, 3.93; N, 11.69; S, 8.92%. Found: C, 70.20; H, 3.90; N, 11.71; S, 8.95%.

9-Chloro-12-methyl-6-(2-thienyl)-12H-indolo[2,3-e][1,4]benzodiazocine (4g).

Yield: 90%; mp 165 ˚C; IR (KBr, cm^{-1}): 3050-2970 (Ar-H), 1620 (C=N), 1590 (C=N), 1570, 1480 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.28 (s, 3H, NCH_3), 5.42 (s, 1H, C=CH), 6.26-8.25 (m, 11H, Ar-H); ^{13}C-NMR(75MHz, $CDCl_3$, δ ppm): 35.40 (NCH_3), 116.17, 116.47, 118.28, 120.36, 122.46, 125.26, 128.19, 129.25, 129.56, 129.62, 129.69, 130.03, 135.45, 138.00, 140.00, 141.61, 142.33, 143.04 (Ar-C), 158.60 (C=N), 162.10 (C=N); MS: Calcd. For $C_{21}H_{14}ClN_3S$: 375.0597. Found: 375.0591. Anal. Calcd for $C_{21}H_{14}ClN_3S$; C, 67.10; H, 3.75; N, 11.18; S, 8.53%. Found: C, 67.12; H, 3.78; N, 11.20; S, 8.50%

General procedure for synthesis of 3-[2-(2-aminoethylimino)2-(2-thienyl) ethylidene]indol-2-ones (7a-c)

To a mixture of 3-(2-oxo-2-(2-thienyl) ethylidene)indol-2-one (**1a,** 0.01 mol) and ethylenediamine (0.01 mol) in distilled water (5.0 ml) , was added TBAB (0.0483g,15 mol %). this reaction mixture was allowed to stir magnetically at 60 ˚c. Progress of the reaction was monitored by TLC (pet.-ether, ethyl acetate = 4:1). The solid obtained was filtered and washed with warm water. It was further purified by crystallization with alcohol to afford pure products, **7a-c**. All the synthesized compounds were well characterized by spectral and elemental analysis.

3-[2-(2-Aminoethylimino)2-(2-thienyl) ethylidene]indol-2-ones (7a).

Yield: 92%; mp 175 ˚C; IR (KBr, cm^{-1}): 3250-3100 (broad, NH_2 and NH), 1650 (C=O), 1610 (C=N), 1550-1400 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.66 (t, 2H, J=5.30, CH_2),

4.06 (t, 2H, J=5.30, CH_2), 6.84 (s, 1H, C=CH), 6.48-7.87 (m, 7H, Ar-H), 9.12 (s, 1H, NH), 10.39 (s, 1H, NH_2); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 37.41 (CH_2), 48.75 (CH_2), 109.04, 116.13, 116.41, 120.54, 122.05, 129.18, 129.49, 129.63, 130.44, 141.55, 142.97, 145.21 (Ar-C), 172.79 (C=O), 163.60 (C=N),; MS: Calcd. For $C_{16}H_{15}N_3OS$: 297.0936. Found: 297.0932. Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13; S, 10.78%. Found: C, 64.65; H, 5.06; N, 14.15; S, 10.80%.

5-Chloro-3-[2-(2-aminoethylimino)2-(2-thienyl)ethylidene]indol-2-ones (7b).

Yield: 90%; mp 122 ˚C; IR (KBr, cm^{-1}): 3280-3110 (broad, NH_2 and NH), 1660 (C=O), 1620 (C=N), 1560-1410 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.68 (t, 2H, J=5.31, CH_2), 4.08 (t, 2H, J=5.31, CH_2), 6.83 (s, 1H, =CH), 6.20-7.86 (m, 6H, Ar-H), 9.13 (s, 1H, NH), 10.40 (s, 1H, NH_2); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 37.62 (CH_2), 48.81 (CH_2), 109.05, 116.14, 116.43, 120.56, 122.06, 129.19, 129.50, 129.65, 130.46, 141.57, 142.98, 145.22, (Ar-C), 164.02 (C=N), 173.01 (C=O); MS: Calcd. For $C_{16}H_{14}ClN_3OS$: 331.0546. Found: 331.0541. Anal. Calcd for $C_{16}H_{14}ClN_3OS$: C, 57.91; H, 4.25; N, 12.66; S, 9.66%. Found: C, 57.95; H, 4.28; N, 12.63; S, 9.68%.

5-Fluoro-3-[2-(2-aminoethylimino)2-(2-thienyl)ethylidene]indol-2-ones (7c).

Yield: 91%; mp 168˚C; IR (KBr, cm^{-1}): 3250-3120 (broad, NH_2 and NH), 1680 (C=O), 1610 (C=N), 1550-1420 (C=C); ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 3.70 (t, 2H, J=5.30, CH_2), 4.09 (t, 2H, J=5.30, CH_2), 6.84 (s, 1H, =CH), 6.25-7.84 (m, 6H, Ar-H), 9.15 (s, 1H, NH), 10.39 (s, 1H, NH_2); ^{13}C-NMR (75MHz, $CDCl_3$, δ ppm): 37.65 (CH_2), 48.79 (CH_2), 109.06, 116.15, 116.45, 120.57, 122.08, 129.21, 129.52, 129.67, 130.47, 141.58, 142.99, 145.24 (Ar-C), 163.12 (C=N), 172.84 (C=O); MS: Calcd. For $C_{16}H_{14}FN_3OS$: 315.0842. Found: 315.0839. Anal. Calcd for $C_{16}H_{14}FN_3OS$: C, 60.94; H, 4.47; N, 13.32; S, 5.07%. Found: C, 60.97; H, 4.45; N,13.35; S, 5.03%.

ANTHELMINTIC ACTIVITY:

Animals: The earthworms, *Pheretima posthuma* collected from moist soil and washed with normal saline to remove all faecal matter were used for the anthelmintic study. The earthworms of 3.0-5.0 cm length and 0.1-0.2 cm width were used for all the experimental protocol due to their anatomical and physiological resemblance with the intestinal roundworm parasites of human beings.

Drugs and chemicals: Albendazole (BANDY, Mankind Pharma Ltd., New Delhi) and Saline water (Claris Life Sciences Ltd., Ahmedabad).

Preparation of suspensions: The suspensions of the synthesized derivatives were freshly prepared before starting the experiment. The appropriately weighed quantity was suspended in saline water to prepare the concentrations of 1% and 2%. Albendazole suspension was used as a reference standard.

Method for activity

Eleven groups, of six earthworms each were released into 10.0 mL of desired formulations as follows; vehicles (normal saline), Albendazole (5.0 mg/mL), or the test suspensions (1%, each) in normal saline.

In the second set of experiment, eleven groups of six earthworms each were released in to 10.0 mL of desired formulations as follows; vehicle (normal saline), albendazole (10.0 mg/mL), or the test suspensions (2% each) in normal saline. Observations included the time taken for paralysis and death of the individual worms. Time for paralysis was noted when no movement of any sort could be observed except when the worms were shaken vigorously.

Time for death of worms were recorded after ascertaining that the worms neither moved when shaken vigorously nor when dipped in warm water (50 °C). Death was concluded when the worms lost their motility followed with fading away of their body colors.

The synthesized 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4]benzodiazocine **(4a-g)** and 3-[2-(2-aminoethylimino)2-(2-thienyl) ethylidene]indol-2-ones (**7a-c**) were screened for anthelmintic activity [29] using *Pheretima posthuma* (Indian earthworms). The results obtained are presented in **Table 1** and were compared with Albendazole as standard at the same concentration. A closer observation reveals that all the synthesized compounds showed moderate to significant activity against *P. posthuma*. It is evident from the experimental data that the compounds **4c** and **4d** exhibited significant anthelmintic activity at 1% and 2% concentrations while compounds **4a**, **4f** and **4g** showed activity equal to that of standard at 1% concentration (paralytic time). Compounds **4a** and **4e** exhibited activity similar to that of standard at 1% concentration (lethal time) and 2% concentration (paralytic and lethal time). Therefore these compounds can be used as anthelmintic agents.

RESULTS AND DISCUSSION:

Chemistry

Appropriate reaction medium is essential consequence to carry out reaction. In our investigation the reaction of 3-(2-oxo-2-(2-thienyl)ethylidene)indol-2-one **1a** with *o*-phenylenediamines as a model reaction was investigated and reaction conditions were optimized using various solvents like methanol, ethanol (neutral/acidic) as well as water with/ without surfactant were screened. The best results with excellent yields in shorter reaction time were obtained in aqueous medium with surfactants. We have carried out the reactions at different temperatures and results are presented in **Table 2**. It is clear that rate of reaction increases with increasing the catalytic concentration up to 15 mol % without any difference on further increasing catalyst. It is noticed that amount of catalyst plays a significant role in controlling the rate of reaction. Therefore among various amounts of the catalyst studied 15 mol % of TBAB was found to be the best at 60 ˚C temperature in aqueous conditions.

It was observed that use of TBAB followed by stirring, the initially floating reactants in the mixture converted to a yellowish-brown turbid emulsion (**Fig. 1a**), which implies the formation of micelle like colloidal aggregates. The light microscopic observation of the emulsion dispersion formed from 3-(2-oxo-2-(2-thienyl) ethylidene)indol-2-one **1a**, *o*-phenylenediamine and TBAB in distilled water shows that spherical particles were formed (**Fig. 1b**). It is assumed that most of the organic substrates are concentrating in the spherical particles which act as a hydrophobic reaction site and result in rapid reaction in water. Reactant **1a** and *o*-phenylenediamine are hydrophobic in aqueous medium. In the miceller solution these escape from water molecule towards the hydrophobic core of the micelle droplets where reaction occurred. The hydrophobic interior of the micelles rapidly excludes the water molecules produced during the reaction and shifts the equilibrium towards the product side. This is shown schematically in **Fig. 2**.

Syntheses of compounds **4a-g** have been performed by taking **1a-g,** *o*-phenylenediamines and tetrabutylammonium bromide in distilled water. The reaction has been carried out by stirring the reaction mixture at 60±2˚c until completion of the reaction as evidenced by TLC. The formation of products **4a-g** were confirmed by the absence of C=O absorption peaks in their IR and ^{13}C-NMR spectra ruling

out the possibilities of the formation of **2** and **3**. ^{1}H-NMR spectra shows peaks at δ 5.46 ppm corresponded to C=CH, 6.40-8.30 ppm corresponded to aromatic protons and 9.20 ppm corresponded to NH **4a**. ^{13}C-NMR spectra shows peaks at δ 156.00 and 160.60 for C=N. Further, in mass spectra M^+ peaks appears at m/z. 327.0830 **4a**. Similar reaction of **1** with ethylenediamine led to the exclusive formation of Schiff's base **7** instead of **5** and **6** in all reaction conditions. The structure of compounds **7** were ascertained by their detailed spectral studies. The IR spectra showed intense carbonyl absorption bands around 1650 cm^{-1}, further ruling out the possibility of product **5** and **6**. It shows broad peak at 3250-3100 cm^{-1} for NH and NH_2. In the ^{1}H-NMR spectra peaks appears at δ 3.82 (t, 2H, J=5.30, CH_2), 3.40 (t, 2H, J=5.30, CH_2) ,6.48 (s, 1H, =CH), 9.12 (s, 1H, NH) and 10.39 (s, 1H, NH_2) ppm. ^{13}C-NMR spectra showed peaks at δ 172.79 (C=O), 163.60 (C=N), 48.75 (CH_2), 37.41 (CH_2) along with aromatic carbons at 145.21-109.04 ppm. Further, mass spectra shows M^+ peak at m/z 297.0936 (**7a)**.

CONCLUSION:

To weave and bind into conclusion, a facile, chemoselective, green synthesis of a novel eight membered ring system *viz.* 6-(2-thienyl)-12*H*-indolo[2,3-e][1,4]benzodiazocine derivatives **4** by the reaction of 3-[2-oxo-2-(2-thienyl)ethylidene]indol-2-ones **1** with *o*-phenylenediamine in water in the presence of TBAB was carried out. However, Schiff base derivatives **7** were obtained under similar conditions with ethylenediamine. Synthesized compounds showed significant activity against *P. posthuma* and can be used as anthelmintic agents.

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REFERENCES:

1. (a) C. J. Li, Chem. Rev. **2005**, 105, 3095-3165; (b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, 35, 209-217; (c) U. M. Lindstrom, *Chem. Rev.* **2002**, 102, 2751-2772; (d) A. Solhy, A. Elmakssoudi, R. Tahir, M. Karkouri, M. Larzek, M. Bousmina, M. Zahouily, *Green Chem.* **2010**, 12, 2261-2267.
2. R. Jain, K. Sharma, D. Kumar, *Tetrahedron Lett.* **2012**, 53, 1993-1997.
3. R. Jain, K. Sharma, D. Kumar, *J. Indian Chem. Soc.* **2014**, 91, 1-7.
4. A. Preetam, M. Nath, *Tetrahedron Lett*. **2016**, 57, 1502-1506.
5. D. Kumar, K. Seth, D. N. Kommi, S. Bhagat, A. K. Chakraborti, *RSC Adv*. **2013**, 3, 15157-15168.
6. R. Jain, K. Sharma, D. Kumar, *Tetrahedron Lett.* **2012**, 53, 6236-6240.
7. S. Naskar, S. Roy, S. Sarkar, *Synth. Commun.* **2014**, 44, 1629-1634.
8. (a) M. Kidwai, A. Jahan, N. K. Mishra, Med. Chem.2014, 4(5), 451-468; (b) R. A. Rane, S. Karunanidhi, K. Jain, M. Shaikh, G. Hampannavar, R. Karpoormath, *Curr. Top. Med. Chem.* **2016**, 16, 1262-1289.
9. C. G. Lima-Junior, G. V. Faheina-Martins, C. C. B. Bomfim, B. B. Dantas, E. P. Silva, D. A. M. de Araujo, E. B. A. Filho, M. L. A. A. Vasconcellos, *Med. Chem*. **2016**, 12, 602-612.
10. B. Bhrigu, D. Pathak, N. Siddiqui, M. S. Alam, W. Ahsan, *Int. J. Pharm. Sci. Drug Res.* **2010**, 2, 229-235.
11. S. Tiwari, *Int. J. Chem. Pharmaceut. Sci.* **2014**, 2, 1225-1240.
12. G. Mathur, S. Nain, *Med. Chem.* **2014**, 4, 417-427.
13. P. Phogat, P. Singh, *Cent. Nerv. Syst. Agents Med. Chem.* **2015**, 15, 28-31.
14. A. S. Grewal, *Int. J. Pharm. Res.* **2014**, 6, 1-7.
15. J. -Y. Ma, Y. -C. Quan, H. -G. Jin, X. -H. Zhen, X. -W. Zhang, L. -P. Guan, *Chem. Biol. Drug. Des.* **2016**, 87, 342-351.
16. H. Ramana, R. Vasanthi, C. P. Kumar, *World J. Pharm. Pharm. Sci.* **2015**, 4, 905-915.
17. H. Ramadoss, D. Saravanan, S. P. N. Sudhan, S. S. Mansoor, *Pharm. Chem.* **2016**, 8, 94-98.
18. S. B. Kumar, M. Ravinder, G. Kishore, V. J. Rao, P. Yogeeswari, D. Sriram, *Med. Chem. Res.* **2014**, 23, 1934–1940.
19. J. Wang, C. Zhu, J. Guo, Z. Zhang, F. Chen, L. Zhang, *Guangdong Huagong* **2015**, 42, 106-113.
20. G. Kulsi, A. Ghorai, P. Chattopadhyay, *Tetrahedron Lett*. **2012**, 53, 3619–3622.
21. P. Singh, A. Dandia, P. Khandelwal, *Indian J. Chem.* **2010**, 49B, 1135-1139.
22. J. George, S. Singh, R. Joshi, R. T. Pardasani, *J. Chem. Sci.* **2013**, 125, 517-524.

23. R. Jain, K. Sharma , D. Kumar, *Helv. Chim. Acta*, **2013**, 96, 414-418.
24. K. Sharma, R. Jain, *J. Serb. Chem. Soc.* **2013**,78, 165-172.
25. K.Sharma, R. Jain, *Turk.J.Chem.* **2013**, 37, 239-251.
26. D. Kumar, L. K. Sharma, K. Sharma, R. Jain, *J. Heterocycl. Chem.* **2017**, 54, 570-574.
27. K. Sharma, R. Jain, *Heterocyclic Lett.* **2017**, 7, 147-153.
28. K. Sharma, L. K. Sharma, R. Jain, *Heterocyclic Lett.* **2015**, 5, 383-390.
29. K. Sharma, R. Jain, *Indian J. Chem.* **2012**, 51B,1462-1469.

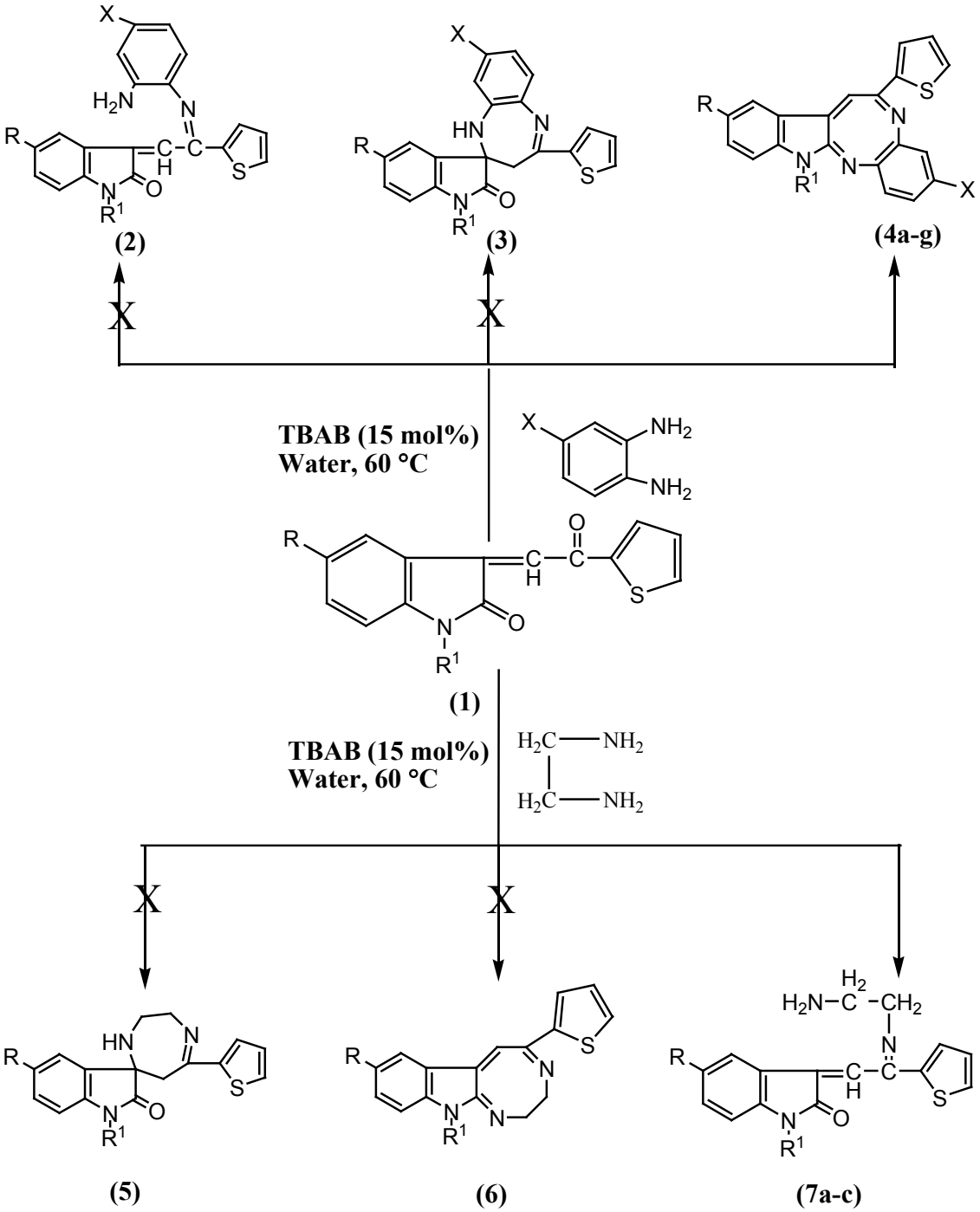
Table 1. Anthelmintic activity of indolo-benzodiazocine derivatives (4a-g) and Schiff's base derivatives (7a-c). (PT- Paralytic time, LT- Lethal time)

S. No.	Compd.	Time (min)			
		Conc. (1%)		Conc. (2%)	
		PT	LT	PT	LT
1.	**4a**	5	7	4	6
2.	**4b**	6	9	5	7
3.	**4c**	4	6	3	5
4.	**4d**	4	6	3	5
5.	**4e**	7	10	6	12
6.	**4f**	5	7	4	6
7.	**4g**	5	7	4	6
8.	**7a**	6	10	6	9
9.	**7b**	6	7	4	6
10.	**7c**	6	7	4	6
11.	**Albendazole (Std.)**	5	7	4	6

Table 2 : **Investigation for the synthesis of 4a under different reaction conditions.**[a]

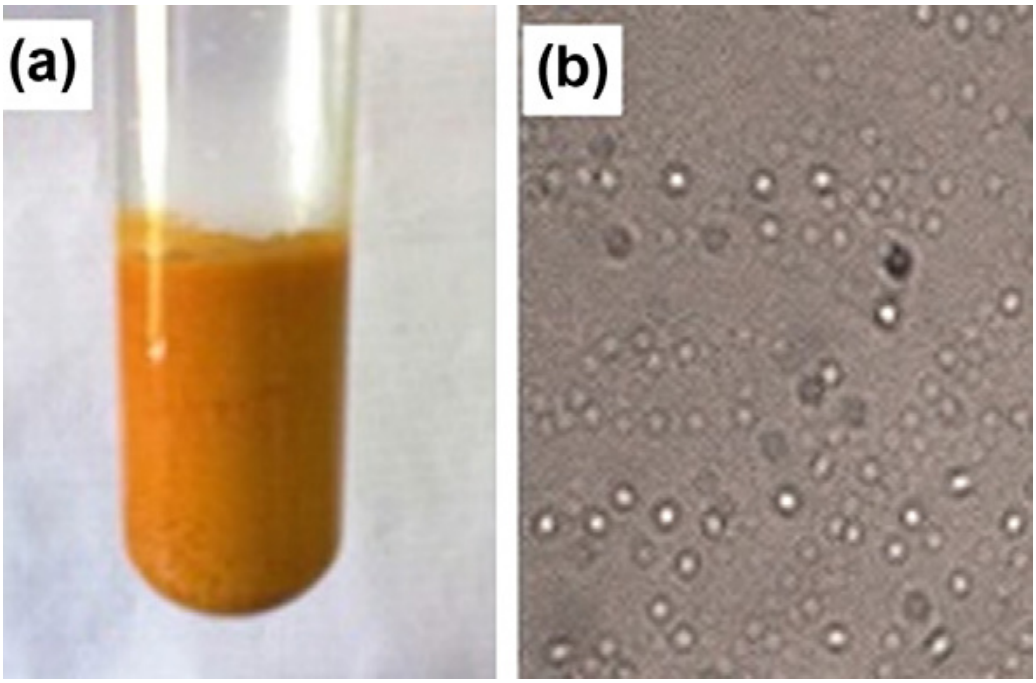
S. No.	Solvent	Temperature (˚C)	Reaction Time (h)	Yield[b] (%)
1.	Methanol	Reflux	4	57
2.	EtOH(neutral)	Reflux	5	55
3.	EtOH(Acidic)	Reflux	4	57
4.	Water	Reflux	3	73
5.	Water /TBAB[c]	RT	6	85
6.	Water /TBAB[c]	60	0.5	85
7.	Water/TBAB[c]	80	0.5	82
8.	Water /TBAB[c]	100	0.5	81
9.	Water /TBAB[c]	Reflux	0.5	78
10.	Water /TBAB[d]	60	0.5	82
11.	Water /TBAB[e]	60	0.5	90
12.	Water /TBAB[f]	60	0.5	91

[a] Reaction conditions: 0.01 mole of **1a** and *o*-phenylenediamine was used.
[b] Isolated yield.
[c] TBAB (10 mol %)
[d]TBAB (5 mol %)
[e] TBAB (15 mol %)
[f] TBAB (20 mol %)



Compd.	R	R^1	X	Compd.	R	R^1	X
4a	H	H	H	**4f**	F	CH_3	H
4b	H	CH_3	H	**4g**	Cl	CH_3	H
4c	F	H	H	**7a**	H	H	-
4d	Cl	H	H	**7b**	Cl	H	-
4e	H	H	CH_3	**7c**	F	H	-

Scheme 1. Synthesis of Compounds **4a-g** and **7a-c**.



(**Fig. 1a**) (**Fig. 1b**)

Figure 1.(a) Reaction mixture of 3-(2-oxo-2-(2-thienyl)ethylidene)indol-2-one **1a** and *o*-phenylenediamine and TBAB in distilled water. (b) Optical micrograph of the reaction mixture (scale bar = 25 µm)

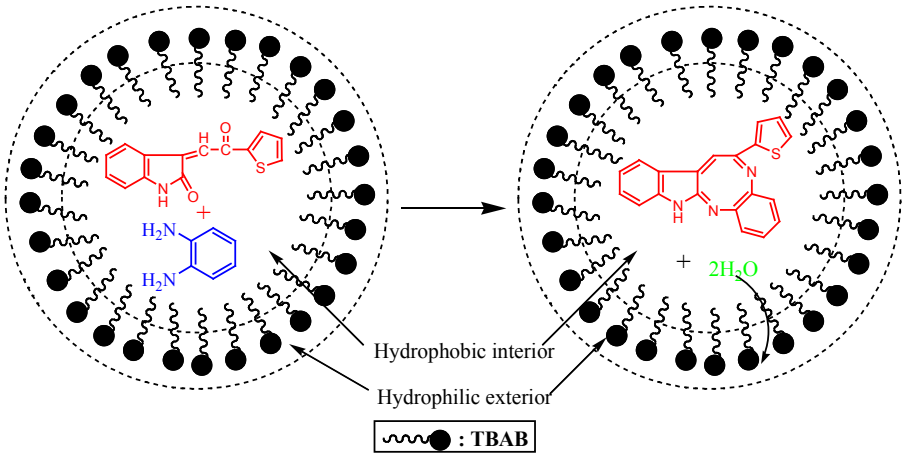


Figure 2.Micelles-promoted green synthesis of 6-(2-thienyl)-12*H*-indolo[2,3-e] [1,4] benzodiazocine.