Environmentally Benign Synthesis of Tetrahydroindeno[1,2-*b*]Pyrrole-3-carboxylate Derivatives as Potential Antiinflammatory Agents

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Srinivas and Ramakrishna: Antiinflammatory Tetrahydroindeno[1,2-*b*]Pyrrole-3-carboxylates

A new series of tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate derivatives(4) were synthesized by reaction of 5-amino-2-mercapto benzimidazole with 1,3-dicarbonyls and activated carbonyl compounds using ceric ammonium nitrate catalyst by a three component one-pot reaction. Structures of these compounds were established on the basis of infrared spectroscopy, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, mass spectrometry and elemental analyses. The title compounds 4a-h were evaluated for antiinflammatory activity using the carrageenan-induced paw edema method at a dose of 100 mg/kg in comparison to ibuprofen as a reference drug. Compounds 4a, 4b, 4c and 4d exhibited potent antiinflammatory activity comparable to that of ibuprofen.

Key words: Tetrahydroindeno[1,2-b]pyrrole-3-carboxylates, multi-component reaction, ceric ammonium nitrate, antiinflammatory activity

Multi-component reactions (MCRs) can be defined as convergent chemical processes where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials[1-5]. In MCRs, a high degree of molecular diversity can be introduced by variation of a single component at a time. Considering that, speed and diversity are key factors in modern drug discovery, MCR strategies offer significant advantages over conventional linear-type syntheses, owing to their exceptional synthetic efficiency[6]. MCRs contribute to the requirements of an eco-friendly process by reducing the number of synthetic steps, energy consumption and waste production. The pyrrole nucleus is widespread in nature, and as previously mentioned, is the key structural fragment

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of heme and chlorophyll, two pigments essential for life. These include some antibacterial 3-halopyrroles such as pentabromopseudodiline and pyoluteorin, both isolated from bacterial sources. Some of the recently isolated pyrrole-containing marine natural products have been found to exhibit considerable cytotoxicity and function as multidrug resistant reversal agent[7]. In addition poly substituted pyrroles are also been used as antioxidants, antibacterial, ionotropic, antitumor, antiinflammatory and antifungal agents[8-13]. It is known that dihydroxy-oxoindeno[1,2-*b*]pyrroles exhibit a wide range of biological activities[14-17]. Eboracin, a substituted indenopyrrole/trioxyindenopyrrole, inhibited the tonic component of convulsive seizures induced in mice by pentylenetetrazol, electroshock or auditory stimulation[18-23].

All melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated 60 F_{254} silica gel plates. Visualization was done by exposing to iodine vapour. Infrared (IR) spectra (KBr pellet) were recorded on a PerkinElmer BX series Fourier transform infrared (FTIR) spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini 300 MHz spectrometer. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values were given in δ ppm with tetramethylsilane as an internal standard. Mass spectral measurements were carried out by electron ionization (EI) method on a Joel JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analysers.

Mixture of 5-amino-2-mercapto-benzimidazole (1) (1 mmol) and 1,3-dicarbonyl (2) (1 mmol) was stirred in ethanol (20 ml) in presence of ceric ammonium nitrate (CAN) 10 mol % at 70° for 10 min. Then activated carbonyl (3) (1 mmol) was added slowly. The reaction mixture was continued stirring for 20 min. After the completion of the reaction (monitored by TLC), the reaction mixture was poured into 20 ml ice cold water. The separated solid is filtered and recrystallized from ethyl acetate to afford the title compounds. The structures of compounds are given in Table 1.

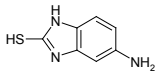
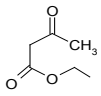
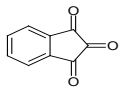
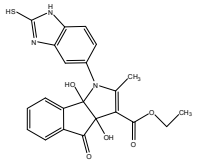
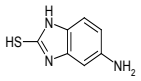
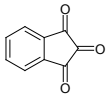
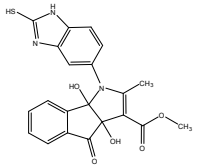
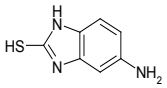
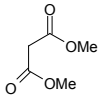
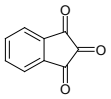
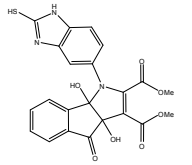
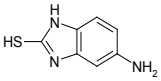
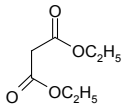
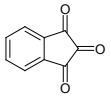
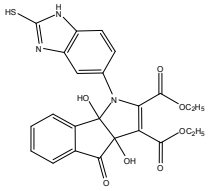
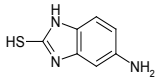
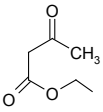
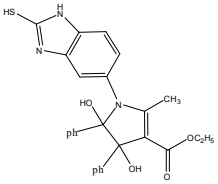
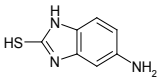
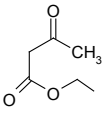
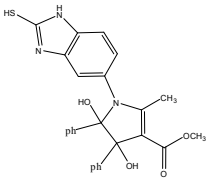
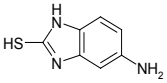
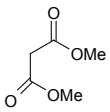
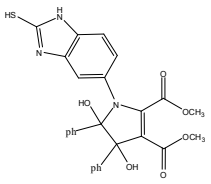
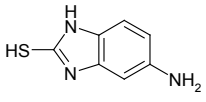
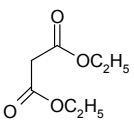
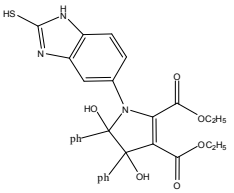
Ethyl-3a,8b-dihydroxy-2-methyl-4-oxo-1-(2-sulfanyl-1H-benzo[d]imidazol-5-yl)-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate (4a); MP 183-185°, yield 91%.^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, 3H, OCH_2CH_3), 2.21 (pyrrole-CH_3), 4.03 (s, 1H, SH), 4.26 (q, 2H, OCH_2CH_3), 4.53(s, 1H, OH, D_2O exchangeable), 4.83 (s, 1H, OH, D_2O exchangeable), 7.00-7.63 (m, 7H, ArH), 8.26 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}:3352 (OH), 3243 (OH), 3140 (NH), 1710, 1680 (CO).^{13}C-NMR (75 MHz, $CDCl_3$) *δ* ppm: 13.43, 14.15, 67.45, 81.01, 90.23, 92.01, 102.11, 114.46, 115.02, 122.23, 125.56, 125.10, 128.12, 133.78, 135.10, 136.15, 140.65, 146.23, 150.12, 168.32, 169.01, 197.23. EI-MS (70 eV) *m/z*:437(M+). Anal. calcd. for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.43; H, 4.45; N, 9.53.

Methyl-3a,8b-dihydroxy-2-methyl-4-oxo-1-(2-sulfanyl-1*H*-benzo[d]imidazol-5-yl)-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate(4b); MP 176-178°, yield 87%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.23 (pyrrole-CH_3), 3.89 (s, 3H, OCH_3), 4.11 (s, 1H, SH), 4.49 (s, 1H, OH, D_2O exchangeable), 4.9 (s, 1H, OH, D_2O exchangeable), 7.13-7.62 (m, 7H, ArH), 8.01 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}: 3341(OH), 3253(OH), 3138(NH), 1735, 1678(CO). ^{13}C-NMR (75MHz, $CDCl_3$) *δ* ppm: 13.95, 52.13, 81.21, 90.12, 93.12, 102.56, 116.91, 117.10, 121.12, 123.10, 125.81, 128.11, 135.12, 133.10, 138.01, 140.18, 147.21, 150.12, 166.34, 169.00, 197.21. EI-MS (70 eV) *m/z*: 423(M+). Anal. calcd. for $C_{21}H_{17}N_3O_5S$: C, 59.45; H, 4.11; N, 9.76. Found: C, 59.57; H, 4.05; N, 9.92.

Dimethyl-3a,8b-dihydroxy-4-oxo-1-(2-sulfanyl-1*H*-benzo[d]imidazol-5-yl)-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-2,3-dicarboxylate(4c); MP 201-203°, yield 80%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.98 (s, 6H, $2OCH_3$), 4.03 (s, 1H, SH), 4.56 (s, 1H, OH, D_2O exchangeable), 4.73 (s, 1H, OH, D_2O exchangeable), 7.08-7.51 (m, 7H, ArH), 8.26 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}:3342 (OH), 3230 (OH), 3146 (NH), 1715, 1700 (CO). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 52.30, 52.83, 84.12, 92.10, 102.34, 116.71, 117.34, 121.02, 122.21, 125.45, 127.34, 128.03, 133.23, 135.71, 138.18, 140.23, 143.54, 150.21, 163.10, 168.12, 169.32, 199.21. EI-MS (70 eV) *m/z*: 467(M+). Anal. calcd. for $C_{22}H_{17}N_3O_7S$: C, 56.61; H, 3.56; N, 8.78. Found: C, 56.53; H, 3.67; N, 8.99.

Diethyl-3a,8b-dihydroxy-4-oxo-1-(2-sulfanyl-1*H*-benzo[d]imidazol-5-yl)-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-2,3-dicarboxylate(4d); MP 193-195°, yield 85%. ^{1}H-NMR ($CDCl_3$, 300 MHz):

TABLE 1: THE STRUCTURES OF THE SYNTHESIZED COMPOUNDS

S. No	5-amino-2-meracpto benzimidazole	1,3-dicarbonyls	Activated carbonyl	Compound
1	 1	 2a	 3a	 4a
2	 1	 2b	 3a	 4b
3	 1	 2c	 3a	 4c
4	 1	 2d	 3a	 4d
5	 1	 2a	 3b	 4e
6	 1	 2b	 3b	 4f
7	 1	 2c	 3b	 4g
8	 1	 2d	 3b	 4h

δ 0.98 (t, 6H, $2OCH_2CH_3$), 4.01 (s, 1H, SH), 4.26 (q, 4H, $2OCH_2CH_3$), 4.53 (s, 1H, OH, D_2O exchangeable), 4.62 (s, 1H, OH, D_2O exchangeable), 7.13-7.49 (m, 7H, ArH), 7.96 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}:3338 (OH), 3263 (OH), 3125 (NH), 1705, 1670 (CO). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm : 14.21, 14.70, 61.34, 61.67, 63.02, 92.23, 102.43, 116.23, 117.32, 120.34, 122.12, 123.05, 127.78, 128.25, 133.45, 135.54, 138.12, 140.17, 142.08, 150.32, 165.10, 168.15, 169.41, 199.10. EI-MS (70 eV) *m/z*: 495 (M+). Anal. calcd. for$C_{24}H_{21}N_3O_7S$: C, 58.21; H, 4.31; N, 8.50. Found: C, 58.18; H, 4.27; N, 8.48.

Ethyl-4,5-dihydroxy-2-methyl-4,5-diphenyl-1-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-4,5-dihydro-1*H*-3-pyrrolecarboxylate (4e); MP 180-182°, yield 93%. ^{1}H-NMR ($CDCl_3$,300 MHz): δ 0.95 (t, 3H, OCH_2CH_3), 2.20 (pyrrole-CH_3), 4.12 (s, 1H, SH), 4.21 (q, 2H, OCH_2CH_3), 4.60 (s, 1H, OH, D_2O exchangeable), 4.81 (s, 1H, OH, D_2O exchangeable), 7.12-7.72 (m, 13H, ArH), 8.01 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}: 3348 (OH), 3240 (OH), 3145 (NH), 1721 (CO). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 13.18, 14.42, 61.07, 99.12, 102.01, 102.21, 104.23, 116.56, 117.04, 124.11, 125.02, 125.44, 126.05, 126.31, 127.00, 127.25, 128.22, 129.09, 129.21, 129.56, 136.34, 140.22, 143.02, 146.05, 148.31, 166.09, 169.20. EI-MS (70 eV) *m/z*: 487(M+). Anal. calcd. for $C_{27}H_{25}N_3O_4S$: C, 66.56; H, 5.19; N, 8.76. Found: C, 66.51; H, 5.17; N, 8.62.

Methyl-4,5-dihydroxy-2-methyl-4,5-diphenyl-1-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-4,5-dihydro-1*H*-3-pyrrolecarboxylate(4f); MP 205-207°, yield 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.21 (pyrrole-CH_3), 3.74 (s, 3H, OCH_3), 4.13 (s, 1H, SH), 4.43 (s, 1H, OH, D_2O exchangeable), 4.58 (s, 1H, OH, D_2O exchangeable), 7.03-7.51 (m, 13H, ArH), 8.06 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}: 3351 (OH), 3243 (OH), 3135 (NH), 1700 (CO). ^{13}C-NMR (75MHz,$CDCl_3$) δ ppm: 13.23, 52.11, 99.10, 102.01, 102.31, 106.08, 114.05, 117.21, 126.01, 126.41, 127.17, 125.21, 128.02, 128.04, 127.22, 127.42, 129.23, 129.90, 129.92, 136.23, 140.21, 143,04, 143.20, 147.42, 166.08, 169.31. EI-MS (70 eV) *m/z*: 473 (M+). Anal. calcd. for $C_{26}H_{23}N_3O_4S$: C, 65.98; H, 4.88; N, 8.75. Found: C, 65.95; H, 4.90; N, 8.87.

Dimethyl-4,5-dihydroxy-4,5-diphenyl-1-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-4,5-dihydro-1*H*-2,3-pyrroledicarboxylate(4g); MP 179-181°, yield 89%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 6H, $2OCH_3$), 4.10 (s, 1H, SH), 4.51 (s, 1H, OH, D_2O exchangeable), 4.64 (s, 1H, OH, D_2O exchangeable), 7.01-7.50 (m, 13H, ArH), 8.00 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}: 3347 (OH), 3242 (OH), 3141 (NH), 1700 (CO). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 51.03, 52.42, 98.32, 101.21, 102.11, 116.21, 117.34, 121.10, 124.09, 124.16, 127.09, 127.18, 127.31, 127.33, 127.54, 128.20, 128.34, 129.03, 129.21, 136.32, 138.11, 143.03, 143.12, 143.14,165.03, 168.21, 169.32. EI-MS (70 eV) *m/z*: 517(M+). Anal. calcd. for $C_{27}H_{23}N_3O_6S$: C, 62.73; H, 4.55; N, 8.22. Found: C, 62.66; H, 4.48; N, 8.12.

Diethyl-4,5-dihydroxy-4,5-diphenyl-1-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-4,5-dihydro-1*H*-2,3-pyrroledicarboxylate(4h); MP. 211-213°, yield 86%.^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.97 (t, 6H, $2OCH_2CH_3$), 4.12 (s, 1H, SH), 4.26 (q, 4H, $2OCH_2CH_3$), 4.51 (s, 1H, OH, D_2O exchangeable), 4.76 (s, 1H, OH, D_2O exchangeable), 7.10-7.62 (m, 13H, ArH), 8.23 (s, 1H, NH, D_2O exchangeable). IR (KBr) cm^{-1}:3341(OH), 3230 (OH), 3142 (NH), 1725 (CO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm:12.09, 13.21, 62.70, 61.40, 98.32, 101.21, 102.92, 114.09, 115.24, 120.31, 126.10, 126.21, 127.26, 127.43, 127.48, 128.12, 129.32, 129.39, 128.45, 128.59, 128.60, 138.12, 140.12, 143.12, 145.20, 147.23, 165.45, 169.02, 171.13. EI-MS (70 eV) *m/z*: 545 (M+). Anal. calcd. for $C_{29}H_{27}N_3O_6S$: C, 63.78; H, 4.50; N, 7.54. Found: C, 63.84; H, 4.99; N, 7.70.

Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity was produced[24,25]. Therefore, we investigated a multi component reaction of 5-amino-2-mercapto-benzimidazole (1), ethyl acetoacetate (2a) and ninhydrine (3a) in ethanol (20 ml), which afforded benzo[*d*]imidazolyltetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate (4a) under the optimized reaction condition, a systematic study was carried out for the catalytic evaluation of CAN in this cyclization. The best overall yield (91%) was obtained with CAN (10 mol%) and is found to be more effective in terms of shorter reaction time (30-40 min) and yield (83-91%). It has been found that these three component process works well for any tested combination of 5-amino-2-meracptobenzimidazole (1), 1,3-dicarbonyls (2) and activated carbonyl compounds (3) in ethanol using 10 mol% CAN as catalyst. By adopting similar procedure,

eight new derivatives (4a-h) have been synthesized by a one-pot three component reaction (Table 1, fig. 1).

The IR spectra of 4a-h showed absorption bands around 3352, 3243 for two OH functional groups, 3140 cm^{-1} for NH functional group and 1710, 1680 cm^{-1} due to C=O functional group. ^1H NMR spectra of compounds 4a-h exhibited four singlets at δ 0.98, 2.21, 4.53 and 4.83 due to OCH_2CH_3, pyrrole-CH_3, and two OH protons, respectively and a quartet at δ 4.26 due to OCH_2CH_3 protons confirms the formation of pyrrole dicarboxylate ring. The structure of the products was elucidated with the help of IR, ^1H NMR, ^{13}C NMR, mass spectrometry (MS) and elemental analyses.

The formation of benzo[*d*]imidazolyl tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylates 4a could be explained by the following plausible

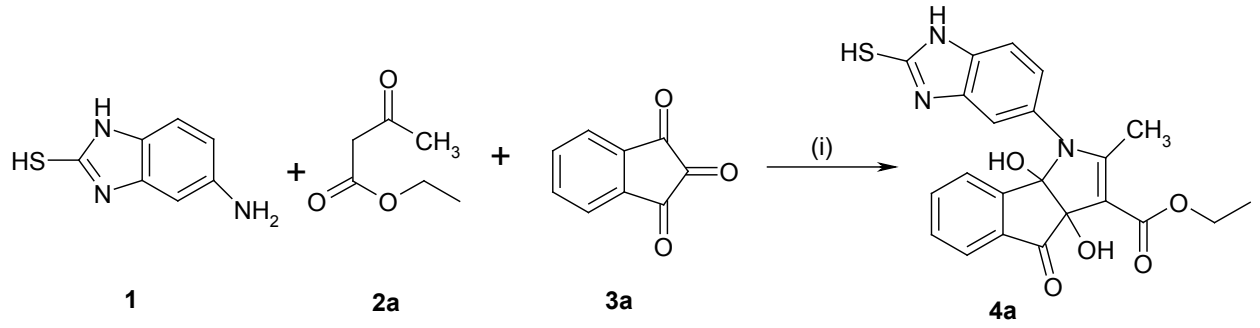


Fig. 1: Synthesis of benzo[*d*]imidazolyltetrahydroindeno[1,2-*b*]pyrrole-3-carboxylates(4a-h)
Reagents and conditions: (i) CAN (10 mol%), ethanol, stirring, 70°, 30 min

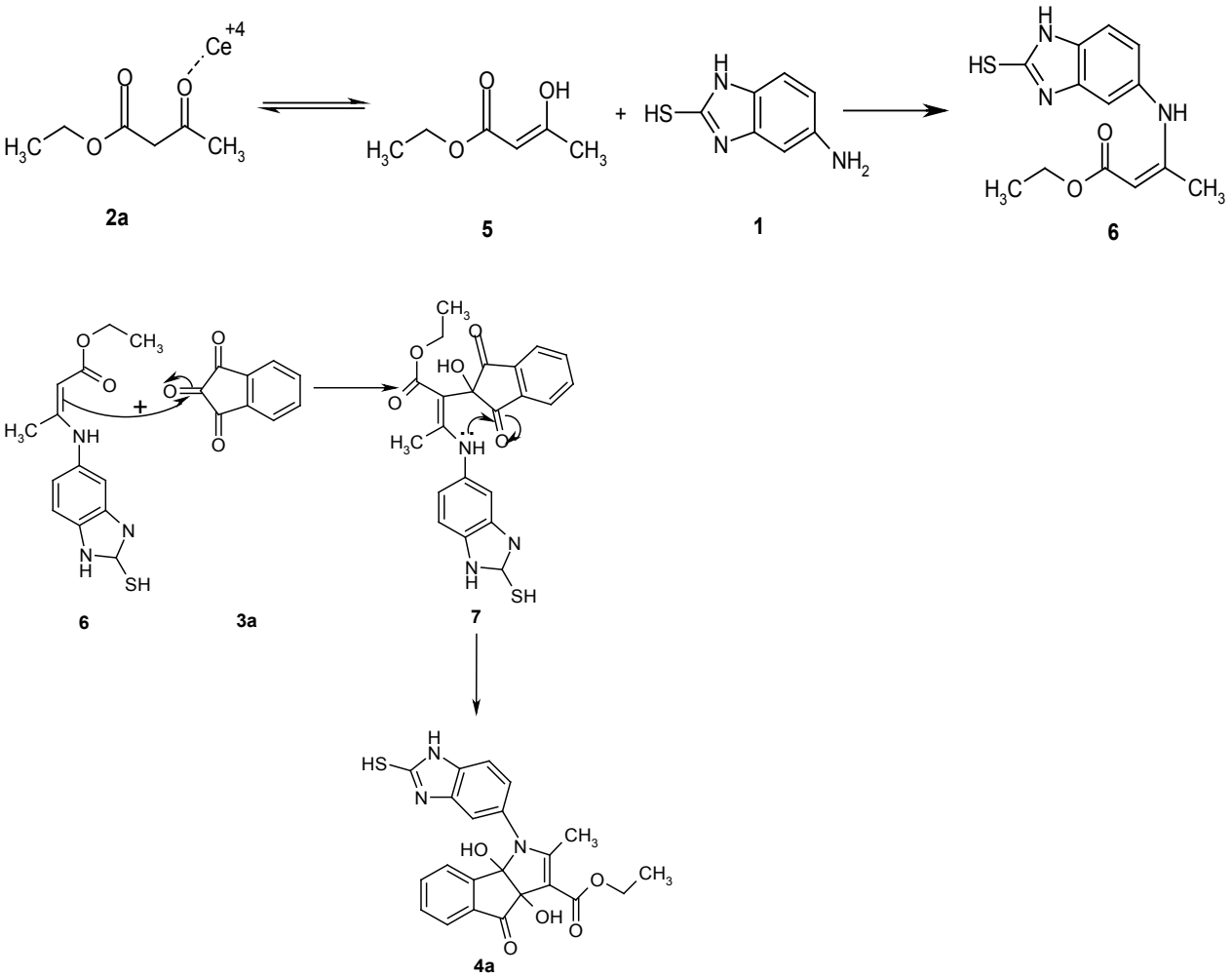


Fig. 2: Plausible mechanism for the formation of benzo[*d*]imidazolyltetrahydroindeno[1,2-*b*]pyrrole-3-carboxylates (4a-h)

mechanism (fig. 2). The reaction involves the initial formation of enaminones 6 between 1,3-dicarbonyl 5 and 5-amino-2-mercaptobenzimidazole 1 activated by CAN. Enaminones 6 react with carboxyl group of ninhydrine 3a via a Michael type addition to form 7, which further undergo cyclization leads to the corresponding title compound. CAN may be activating the double bond of 1,3-dicarbonyl 2a by forming a complex, there by the reaction is facilitated and also enhances the rate of reaction.

Antiinflammatory activity was determined in the carrageenan-induced rat paw edema model[26]. Wistar rats of either sex weighing 150-200 g were divided into 6 groups (n=6) and they were fasted 18 h before the experiment with water *ad libitum*. Group I received 1% sodium carboxymethyl cellulose (CMC) (negative control), group II received ibuprofen at a dose of 100 mg/kg (positive control) and groups III to VI were given the compounds 4a-h (100 mg/kg). All the compounds 4a-h were given in oral route. After 30 min, 0.1 ml of 1% carrageenan suspension in normal saline was injected into the sub plantar region of the left hind paw of each rat to induce edema. The edema volumes of the injected paw measured with the help of plethysmograph at the interval of 0, 1, 2, 4 and 6 h. The difference between the paw volumes of treated animals were compared with that of the control group and the mean edema volume was calculated. Percentage inhibition was calculated as per the Eqn., percent inhibition = (Vo–Vt)/Vo)×100, where, Vo=volume of the paw control at time t, Vt=volume of the paw of drug treated at time t. Results were expressed as a mean±SE. The antiinflammatory properties were recorded at successive intervals of 0, 1, 2, 4 and 6 h and compared with that of standard ibuprofen. The antiinflammatory activity data (Table 2) indicated that all the compounds 4a-h exhibited significant activity by decreasing the paw volume that was produced by carrageenan. Among all the compounds tested, it is interesting to note that the compounds 4a, 4b, 4c and 4d showed better antiinflammatory activity, may be due to the basic skeleton indeno[1,2-*b*]pyrrole-3-carboxylate.

In conclusion, the synthesis of novel benzo[*d*]imidazolyltetrahydroindeno[1,2-*b*]pyrrole-3-carboxylates was achieved through a one step process from readily accessible starting materials in moderate to good yields. This synthesis benefits from a simple method of purification, which does not require chromatography. The ease of purification complimented this synthetic technology practical, easy to perform and facile. The title compounds can be considered as future drug candidates for antiinflammatory activity by simple modifications in their structure and of course required further evaluations to reveal the exact mechanism of action, so that using structure activity relationship a new potent analogue can be generated with desired efficacy. The newly synthesized novel benzo[d]imidazolyl-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylates were tested for antiinflammatory activity and compounds 4a, 4b, 4c and 4d exhibited significant activity, when compared to standard.

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Conflict of interests:

Authors report no conflict of interests.

TABLE 2: ANTIINFLAMMATORY ACTIVITY OF TETRAHYDROINDENO[1,2-*b*]PYRROLE-3-CARBOXYLATES[#] (4a-h)

	Paw volume (ml of Hg)[b]				
Group[a]	0 h	1 h	2 h	4 h	6 h
4a	0.18±0.03	0.55±0.07	0.55±0.05	0.52±0.01	0.37±0.05***
4b	0.21±0.01	0.42±0.03	0.58±0.04	0.50±0.02	0.30±0.02***
4c	0.15±0.01	0.40±0.05	0.51±0.01	0.59±0.01	0.40±0.02
4d	0.18±0.03	0.58±0.1	0.50±0.04	0.52±0.01	0.41±0.07
4e	0.37±0.02	0.63±0.08	0.57±0.02	0.53±0.06	0.46±0.01
4f	0.41±0.07	0.59±0.02	0.60±0.05	0.60±0.02	0.31±0.05
4g	0.44±0.05	0.52±0.04	0.92±0.04	0.61±0.07	0.47±0.03
4h	0.58±0.01	0.57±0.02	0.81±0.02	0.55±0.01	0.57±0.02
Control	0.36±0.3	0.90±0.05	1.07±0.08	1.2±0.05	0.96±0.03
Ibuprofen	0.30±0.5	0.66±0.03	0.70±0.05***	0.60±0.05***	0.40±0.05***

[a]Dose levels: test compound (100 mg/kg b.w) ibuprofen (100 mg/kg b.w), [b]values are expressed as mean±SE. Statistically significant compound to respective control value. ***P<0.001 compared to control. [#]n=6, number of animals used in each group

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