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Synthesis and anti-inflammatory and analgesic activity of 5-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(3,5-dimethyl-4-isoxazolyl)-2-aryl-thiazolidin-4-ones

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A new series of 5-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(3,5-dimethyl-4-isoxazolyl)-2-aryl-thiazolidin-4-ones **4** have been accomplished by a simple synthetic protocol. The reaction of 4-benzalamino-3,5-dimethylisoxazoles **3** with mercapto succinic acid furnishes 2-(3-(3,5-dimethyl-4-isoxazolyl)-4-oxo-2-aryl thiazolidin-5-yl) acetic acids **3**, which are then cyclized to the title compounds *viz*., isoxazolyl thiazolyl benzimidazoles **4** on treatment with 1,2-phenylene diamines. The title compounds **4** have been screened for their anti-inflammatory and analgesic activity.

Keywords: Isoxazolyl thiazolyl benzimidazoles, cyclocondensation, anti-inflammatory activity, analgesic activity

Benzimidazole is an important nucleus that has been extensively used in medicinal chemistry, notable examples being the antihistaminic asterizole and the antiulcerative omeprazole[1]. Benzimidazoles are also known for their anti-inflammatory[2], antibiotic[3], antihelmintic[4], anticancer[5], and antiviral activities[6]. Thiazolidinones and their derivatives has received much attention due to wide range of biological activities such as antioxidant[7], anti-inflammatory and analgesic[8], antitumor[9], antitubercular[10], arthritis[11], antimicrobial[12], antidiabetic[13] activity. Thiazolidinone derivatives have been found to exhibit NSAIDs activity through the selective COX-2 inhibitory mechanism[14], and were found to be more potent than reference drugs. A large number of isoxazole derivatives exhibited analgesic and anti-inflammatory[15], anti-convulsant[16], anticancer[17], antibacterial[18] and antitubercular[19] activities.

Molecular hybridization is a relatively new concept in the field of drug design, and development involving the fusion of two or more pharmocophoric submits which have an inhibitory effect against the target disease. The newly designed structure can lead to compounds having improved affinity and effects than the parent compounds with reduced side effects, while retaining the desired characteristics of original template[20-22]. Prompted by these reports, the researchers are interested to construct isoxazolyl thiazolyl benzimidazole hybrids by utilizing a simple synthetic protocol to evaluate the anti-inflammatory and analgesic activities of these compounds. Synthesis and anti-inflammatory and analgesic activity of 5-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(3,5-dimethyl-4-isoxazolyl)-2-aryl-thiazolidin-4-ones have been reported.

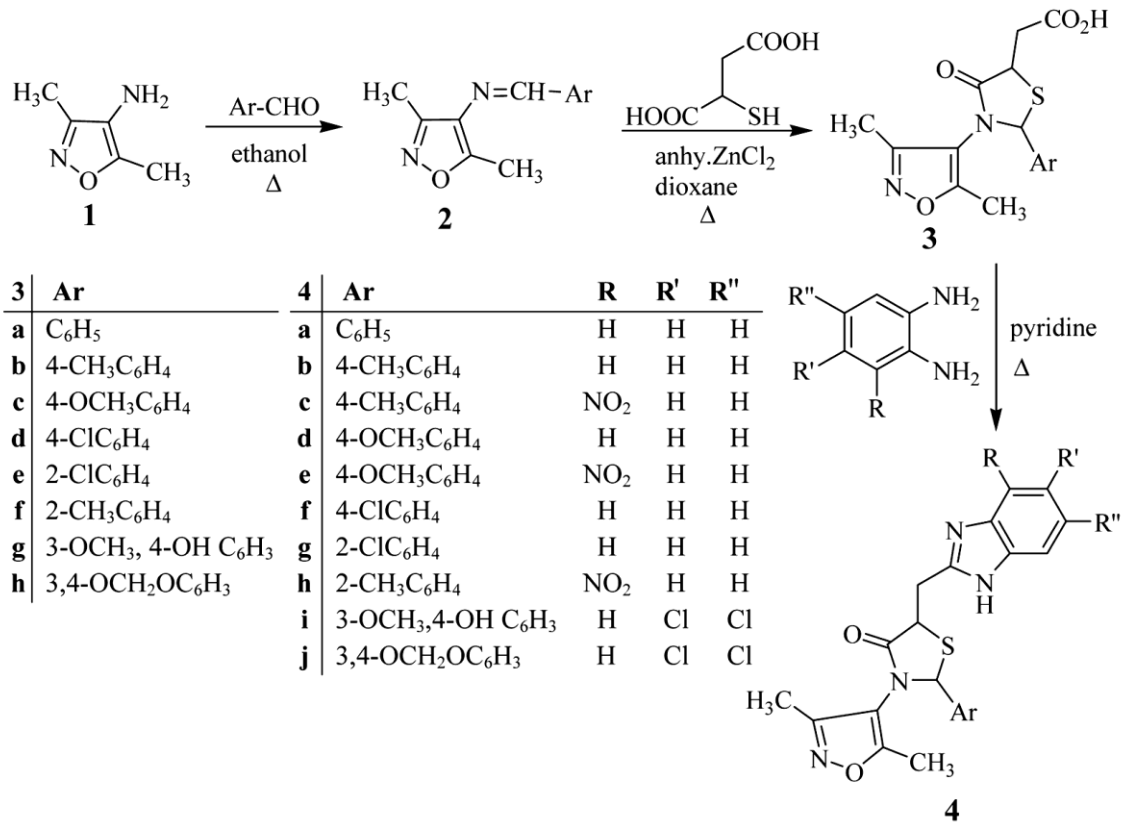
Results and Discussion

Chemistry

The synthesis of title compounds **(4)** was accomplished by the synthetic sequence shown in the Scheme I. The reaction of 4-benzalamino-3,5-dimethyl isoxazoles **(2)**[23] with mercapto succinic acid in presence of traces of anhy. $ZnCl_2$ in dioxane afforded the corresponding 2-(3-(3,5-dimethyl-4-isoxazolyl)-4-oxo-2-aryl thiazolidin-5-yl) acetic acids **(3)** by cyclocondensation. Isoxazolyl thiazolidin-4-ones **(3)** possessing acetic acid side chain, on treatment with 1,2-phenylene diamines in pyridine underwent cyclocondensation to furnish the title compounds *viz*., 5-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(3,5-dimethyl-4-isoxazolyl)-2-aryl-thiazolidin-4-ones **(4)**.

The structures of the newly synthesized compounds **3** and **4** were established by spectral and analytical data (Table I and Table II).

IR spectra of isoxazolyl acetic acids **(3)** exhibited strong absorption bands at 1680 and 1700 cm^{-1} due to carbonyl group and 3350 cm^{-1} due to OH group stretching vibrations respectively. ^{1}H NMR spectra of **(3)** displayed two distinct signals as a triplet at δ 4.5 and a doublet at δ 3.2 due to COCHS and CH_2 protons respectively. The lone -N-CH-Ar proton resonated as a singlet at δ 5.6, whereas -COOH proton appeared as a broad singlet at δ 10.5, which is D_2O exchangeable.



3	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$OCH_3C_6H_4$
d	4-ClC_6H_4
e	2-ClC_6H_4
f	2-$CH_3C_6H_4$
g	3-OCH_3, 4-OH C_6H_3
h	3,4-$OCH_2OC_6H_3$

4	Ar	R	R'	R''
a	C_6H_5	H	H	H
b	4-$CH_3C_6H_4$	H	H	H
c	4-$CH_3C_6H_4$	NO_2	H	H
d	4-$OCH_3C_6H_4$	H	H	H
e	4-$OCH_3C_6H_4$	NO_2	H	H
f	4-ClC_6H_4	H	H	H
g	2-ClC_6H_4	H	H	H
h	2-$CH_3C_6H_4$	NO_2	H	H
i	3-OCH_3,4-OH C_6H_3	H	Cl	Cl
j	3,4-$OCH_2OC_6H_3$	H	Cl	Cl

Scheme I

Table I — Anti-inflammatory activity of compounds **4a-j**

Compd	Volume of edema[b] (% inhibition)			
	1 h	2 h	3 h	4 h
4a	72.2 ± 3.6	84.1 ± 8.4	88.2 ± 4.6	91.0 ± 6.2
4b	52.1 ± 3.9	66.5 ± 7.2[c]	71.2 ± 5.4[c]	78.6 ± 3.4
4c	50.8 ± 5.2	69.8 ± 4.5[c]	74.6 ± 5.7[c]	86.4 ± 6.2
4d	50.1 ± 3.8	81.7 ± 6.9	81.1 ± 5.4	76.6 ± 3.2[c]
4e	52.1 ± 4.4	56.1 ± 5.7[c]	61.8 ± 3.7[c]	77.1 ± 2.8
4f	60.1 ± 7.9	68.0 ± 4.5[c]	67.4 ± 7.2[c]	72.0 ± 7.4[c]
4g	58.2 ± 6.1	71.2 ± 2.6[c]	78.6 ± 3.6[c]	77.1 ± 7.6[c]
4h	51.4 ± 7.1	59.6 ± 7.3	61.2 ± 4.2[c]	66.5 ± 4.8[c]
4i	67.2 ± 7.5	81.5 ± 7.6	80.9 ± 3.4	81.2 ± 6.4
4j	70.2 ± 3.5	73.5 ± 2.6	81.2 ± 3.5	85.5 ± 6.0
Control	59.2 ± 6.4	89.4 ± 7.3	96.2 ± 2.5	91.2 ± 2.3
Indomethacin	48.8 ± 5.0	43.6 ± 4.9	46.4 ± 4.3	47.8 ± 5.4

[a] Dose levels, PO: test compound(10 mg/kg b.wt) Indomethacin (10 mg/kg b.wt)
[b] Values are expected as means ± S.E. (number of rats N=6 rats)
[c] Statistically significant compared to respective control values, P<0.05 (Dunnett's test)

Table II — Analgesic activity of compounds **4a-j**

Compd	Reaction time (sec) (%inhibition)		
	0 h	1 h	2 h
4a	15.2 ± 1.86	16.5 ± 1.75	16.6 ± 2.31
4b	18.6 ± 2.30	23.6 ± 2.84[c]	25.3 ± 2.82[c]
4c	15.6 ± 1.92	25.6 ± 2.82[c]	21.8 ± 1.02[c]
4d	19.9 ± 2.69	18.2 ± 2.81[c]	20.1 ± 2.68
4e	17.9 ±2.53	23.5 ± 2.82[c]	11.2 ± 1.82[c]
4f	15.9 ± 1.92	20.9 ± 1.23[c]	17.2 ± 1.91[c]
4g	17.5 ± 2.04	22.7 ± 2.61[c]	22.8 ± 2.38[c]
4h	15.4 ±1.56	20.1 ± 2.21	20.9 ± 2.18[c]
4i	16.9 ± 2.63	14.7 ± 1.23	22.5 ± 0.83[c]
4j	20.1 ± 1.80	23.6 ± 1.50	25.5 ± 0.75
Control	16.4 ± 0.65	16.2 ± 0.85	16.4 ± 1.20
Indomethacin	17.3 ± 0.80	21.8 ± 0.34	22.4 ± 0.30

[a] Dose levels, PO: test compound(10 mg/kg b.wt) Indomethacin (10 mg/kg b.wt)
[b] Values are expected as means ± S.E(number of rats N=6 rats)
[c] Statistically significant compared to respective control values, P<0.05(Dunnett's test)

The mass spectrum of **(3a)** exhibited the molecular ion $[M+H]^+$ peak at *m/z* 333 confirming cyclization. IR spectra of isoxazolyl thiazolyl benzimidazoles **(4)** exhibited strong absorption bands at 1680 and 3295 cm^{-1} due to carbonyl and NH functional groups stretching vibrations respectively. The absence of 1700 and 3350 cm^{-1} absorption bands in the IR spectra of **(4)** clearly confirms the cyclization, which are present in its precursor due to C=O and OH groups respectively.(**3**). ^1H NMR spectra of **(4)** showed a characteristic singlet at δ 9.0, which is D_2O exchangeable due to benzimidazole NH proton

confirming cyclization. The mass spectrum of **(4a)** displayed a molecular ion $[M+H]^+$ peak at *m/z* 405. Elemental analyses are also confirmed with the structures proposed for compounds **3** and **4**.

Anti-inflammatory activity

The anti-inflammatory activity of newly synthesized compounds **4a-j** was evaluated by Carrageenan-induced paw edema method in rats[24] using Indomethacin as a standard drug. The anti-inflammatory activity data (Table I) indicated that all the test compounds caused significant inhibition of paw edema response. Compounds **4b, 4e, 4f,** and **4h** caused significant decrease in paw edema after 2,3, and 4 h drug administration by causing inhibition to the extent of 25%, 37%, 29%, and 36% respectively, while compounds **4c** and **4g** gave their response after 2 h of administration and continued to the third hour by causing inhibition to the extent of 22%, and 20% respectively. On the other hand, compounds **4a, 4d, 4i,** and **4j** were inactive towards Carrageenan-induced paw edema causing inhibition only to the extent of 8%, 16%, 15%, and 17% respectively in comparison with reference drug Indomethacin (inhibition 17%). Thus compounds **4b, 4e, 4f,** and **4h** exhibited good anti-inflammatory activity. Among all the test compounds, it is important to note that compounds **4e** and **4h** showed best anti-inflammatory activity.

Analgesic activity

The analgesic activity of newly synthesized compounds **4a-j** were evaluated by hot plate method[25] using Indomethacin as a reference drug. Methods of statistical analysis were done according to Armitage *et al*.[26] The analgesic activity was measured at 0, 1 and 2 h time intervals after pain induction. The analgesic activity data (Table II) indicated that the test compounds exhibited moderate to good analgesic activity .Compounds **4b, 4c, 4e, 4g,** and **4j** showed significant analgesic activity by causing inhibition to the extent of 23%, 25%, 23%, 22%, and 23% respectively compared to reference drug Indomethacin (inhibition 21%), after 1 h post-administration and 25%, 21% 11%, 22%, and 25% respectively after 2 h post-administration. Compounds **4d, 4f,** and **4g** exhibited slightly less activity than Indomethacin (inhibition 21%) by causing inhibition to the extent of 18%, 20%, and 22% respectively, whereas compounds **4a** and **4i** have least analgesic activity with inhibition of 16% and 14% respectively. Thus compounds **4b, 4c, 4e,** and **4j** have good analgesic activity. Among all the test compounds it is important to note that compounds **4b** and **4j** showed good analgesic activity.

Experimental Section

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on a Merck precoated 60 F_{254} silica gel plates. Visualization was carried out by exposure to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Brucker 300 MHz spectrometer using TMS as internal standard (Chemical shift values are given in δ ppm). Mass spectra were scanned on a Agilent LC-MSD mass spectrometer. C, H, N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model analyzers. 3,5-Dimethyl-4-aminoisoxazole was purchased from Sigma-Aldrich chemicals, USA.

General procedure for the synthesis of 2-(3-(3,5-dimethyl-4-isoxazolyl)-4-oxo-2-aryl thiazolidin-5-yl) acetic acids, 3

4-Benzalamino-3,5-dimethylisoxazole **(2)** (0.01 mol), mercapto succinic acid (0.01 mol) were taken in dioxane (15 mL). To this traces of anhyd. $ZnCl_2$ was added and the contents are refluxed in a Dean-Stark apparatus for 6 h. The reaction mixture was cooled and poured on to ice-cold water. The separated product was filtered and recrystallized from ethanol.

3a: Yield 80%. m.p. 90-92°C. IR (KBr): 1680 (C=O), 1700 (C=O), 3355 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.2 (d, 2H, CH_2), 4.5 (t, 1H, COCHS), 5.6 (s, 1H, N-CH-Ar), 7.2-7.6 (m, 5H, Ar-H), 10.8 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 333 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{16}N_2O_4S$; C, 57.83; H, 4.81; N, 8.43. Found: C, 57.86; H, 4.85; N, 8.40%.

3b: Yield 75%. m.p. 100-102°C. IR (KBr): 1675 (C=O), 1700 (C=O), 3350 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 4.4 (t, 1H, COCHS), 5.7 (s, 1H, N-CH-Ar), 7.1-7.3 (d, 2H, Ar-H), 7.4-7.6 (d, 2H, Ar-H), 10.8 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 347 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_4S$; C, 58.95; H, 5.20; N, 8.09. Found: C, 58.92, H, 5.23, N, 8.07%.

3c: Yield 70% m.p. 96-98°C. IR (KBr): 1670 (C=O), 1705 (C=O), 3340 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.5 (t, 1H,

COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.2 (d, 2H, Ar-H), 7.3-7.4 (d, 2H, Ar-H), 10.5 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 363 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_5S$ C, 56.35; H, 4.97; N, 7.73. Found: C, 56.38, H, 4.94, N, 7.72%.

3d: Yield 75%. m.p.135-37°C. IR (KBr): 1670 (C=O), 1700 (C=O), 3350 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 4.5 (t, 1H, COCHS), 5.6 (s, 1H, N-CH-Ar), 7.2-7.7 (m, 4H, Ar-H), 10.7 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 367 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{15}N_2O_4SCl$: C, 52.45; H, 4.09; N, 7.65. Found: C, 52.48, H, 4.11, N, 7.62%.

3e: Yield 65%. m.p. 140-42°C. IR (KBr): 1675 (C=O), 1700 (C=O), 3345 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.0 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.5 (d, 2H, CH_2), 4.6 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.2-7.6 (m, 4H, Ar-H), 10.8 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 367 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{15}N_2O_4SCl$: C, 52.45; H, 4.09; N, 7.65. Found: C, 52.42, H, 4.06, N, 7.68%.

3f: Yield 65%. m.p. 111-13°C. IR (KBR): 1670 (C=O), 1705 (C=O), 3340 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 3.4 (d, 2H, CH_2), 4.5 (t, 1H, COCHS), 5.6 (s, 1H, N-CH-Ar), 7.2-7.7 (m, 4H, Ar-H), 10.7 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 347 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.95; H, 5.20; N, 8.09. Found: C, 58.98, H, 5.18, N, 8.11%.

3g: Yield 72%. m.p. 120-22°C IR (KBr): 1665 (C=O), 1695 (C=O), 3350 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.6 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.2-7.5 (m, 3H, Ar-H), 10.1 (bs, 1H, OH, D_2O exchangeable), 10.9 (bs, 1H, COOH, D_2O exchangeable); ESI-MS: *m/z* 379 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.76; N, 7.40. Found: C, 53.99, H, 4.79, N, 7.43%.

3h: Yield 73%. m.p. 127-29°C. IR (KBr): 1670 (C=O), 1700 (C=O), 3340 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 4.0 (s, 2H, -OCH_2O), 4.6 (t, 1H, COCHS), 5.6 (s, 1H, N-CH-Ar), 7.2-7.5 (m, 3H, Ar-H), 10.8 (bs, 1H, OH, D_2O exchangeable); ESI-MS: *m/z* 377 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.25; N, 7.44. Found: C, 54.22, H, 4.22, N, 7.48%.

General procedure for the synthesis of 5-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(3,5-dimethyl-4-isoxazolyl)-2-aryl-thiazolidin-4-ones, 4

Isoxazolyl thaizolyl acetic acids **(3)** (0.01 mmol) and 1,2-phenylene diamines (0.01 mmol) were dissolved in pyridine (15 mL), and the contents are refluxed for 5 h. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled and poured over ice-cold water with stirring. The separated solid was filtered, washed with water dried and, recrystallized from methanol.

4a: Yield 75%. m.p. 125-27°C. IR (KBr): 1680 (C=O), 3285 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 4.5 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.1-7.7 (m, 9H, Ar-H), 9.0 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 405 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{20}N_4O_2S$: C, 65.34; H, 4.95; N, 13.86. Found: C, 65.30; H, 4.92; N, 13.85%.

4b: Yield 70%. m.p. 134-36°C. IR (KBr): 1685 (C=O), 3295 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.5 (d, 2H, CH_2), 4.6 (t, 1H, COCHS), 5.4 (s, 1H, N-CH-Ar), 7.0-7.8 (m, 8H, Ar-H), 9.5 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 419 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{22}N_4O_2S$: C, 66.02; H, 5.26; N, 13.39. Found: C, 66.05; H, 5.28; N, 13.37%.

4c: Yield 70%. m.p. 150-52°C IR (KBr): 1665 (C=O), 3275 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 3.4 (d, 2H, CH_2), 4.5 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.7 (m, 7H, Ar-H), 9.3 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 464 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{21}N_5O_4S$: C, 59.61; H, 4.53; N, 15.11. Found: C, 59.64; H, 4.56; N, 15.14%.

4d: Yield 75%. m.p. 140-42°C. IR (KBr): 1670 (C=O), 3300 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.5 (d, 2H, CH_2), 3.7 (s, 3H, OCH_3), 4.5 (t, 1H, COCHS), 5.4 (s, 1H, N-CH-Ar), 7.1-7.8 (m, 8H, Ar-H), 9.5 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 435 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{22}N_4O_3S$: C, 63.59; H, 5.06; N, 12.90. Found: C, 63.56; H, 5.09; N, 12.92%.

4e: Yield 70%. m.p. 145-47°C. IR (KBr): 1670 (C=O), 3285 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.5 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.8 (m, 7H, Ar-H), 9.1 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 480 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{21}N_5O_5S$: C, 57.62; H, 4.38; N, 14.61. Found: C, 57.60; H, 4.35; N, 14.64%.

4f: Yield 70%, 165-67°C. IR (KBr): 1675 (C=O), 3310 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1

(s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.2 (d, 2H, CH_2), 4.4 (t, 1H, COCHS), 5.4 (s, 1H, N-CH-Ar), 7.0-7.7 (m, 8H, Ar-H), 9.0 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 439 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{19}N_4O_2SCl$: C, 60.27; H, 4.33; N, 12.78. Found: C, 60.29; H, 4.35; N, 12.80%.

4g: Yield 70%. m.p. 160-62°C. IR (KBr): 1670 (C=O), 3300 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.2 (d, 2H, CH_2), 4.2 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.7 (m, 8H, Ar-H), 9.2 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 439 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{19}N_4O_2SCl$: C, 60.27; H, 4.33; N, 12.78. Found: C, 60.24; H, 4.30; N, 12.76%.

4h: Yield 75%. m.p. 155-57°C. IR (KBr): 1675 (C=O), 3290 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, Ar-CH_3), 3.3 (d, 2H, CH_2), 4.4 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.5 (m, 7H, Ar-H), 9.0 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 464 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{22}N_4O_2S$: C, 66.02; H, 5.26; N, 13.39. Found: C, 66.05; H, 5.28; N, 13.37%.

4i: Yield 65%. m.p. 170-72°C. IR (KBr): 1670 (C=O), 3295 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.5 (t, 1H, COCHS), 5.6 (s, 1H, N-CH-Ar), 7.0-7.5 (m, 5H, Ar-H), 9.0 (bs, 1H, NH, D_2O exchangeable), 9.8 (bs, 1H, OH, D_2O exchangeable); ESI-MS: *m/z* 519 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{20}N_4O_4SCl_3$: C, 53.28; H, 3.86; N, 10.81. Found: C, 53.24; H, 3.89; N, 10.83%.

4j: Yield 65%. m.p. 176-78°C. IR (KBr): 1675 (C=O), 3300 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 4.0 (s, 2H, OCH_2O), 4.5 (t, 1H, COCHS), 5.5 (s, 1H, N-CH-Ar), 7.0-7.6 (m, 5H, Ar-H), 9.3 (bs, 1H, NH, D_2O exchangeable); ESI-MS: *m/z* 517 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{18}N_4O_4SCl_2$: C, 53.48; H, 3.48; N, 10.85. Found: C, 53.45; H, 3.45; N, 10.88%.

Anti-inflammatory activity

The albino rats weighing between 150 and 180 g were used for anti-inflammatory activity by Carragenon induced rat wind paw method. They were kept in animal house under standard conditions of light and temperature with free access to food and water. The rats were randomly divided into 12 groups, with six animals in each group. One group was kept as control, another group received the standard drug Indomethacin (at a dose of 10 mg/kg B. W. P.O) the rest were treated with test compounds which were dissolved in 0.05 mL solution of DMSO. Edama was induced in all groups of animals by subplanatar injection of Carragenon solution in normal saline of left hind paw under light ether anaesthesia, 1 h after oral administration of test compounds. The paw volume was recorded by plethysmograph at 1,2,3 and 4 h. after administration of DMSO. The edema was expressed as an increase in the volume of paw, and the % of edema inhibition for each rat and each group was calculated as follows:

$$\%\text{Inhibition} = \frac{(v_t - v_o)\ \text{control} - (v_t - v_o)\ \text{test compound} \times 100}{(v_t - v_o)\ \text{control})}$$

Where v_t = volume of edema at specific time
$v_\circ$ = volume of edema at zero time interval

Analgesic activity

Albino rats weighing 150-180 g were used for evaluation of analgesic activity by Hot Plate method. They were kept in animal house under standard conditions of light and temperature with free access to food and water. The animals were randomly divided into 12 groups, with six animals in each group. One group was kept as a control, and another group received the standard drug Indomethacin (at a dose of 10mg/kg B.W. P. O), and remaining groups were treated with test compounds (10mg/kg b. w.) orally. The paws of rats are very sensitive to heat at a temperature which does not damage the skin. The responses are jumping, withdrawal of the paws and licking of the paws. The animals are placed on the hot plate and observations were recorded at the time interval of 0, 1, and 2 h. The recorded values were the average of six administrations ± S.E. and the percentage inhibition of the comparison with the basal values.

Conclusion

In conclusion, a simple and efficient protocol for the synthesis of isoxazolyl thiazolyl benzimidazoles has been described. The title compounds have been evaluated for their anti-inflammatory and analgesic activities. Some of the newly synthesized compounds exhibited remarkable activity in comparison with reference drugs.

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