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DRUG SYNTHESIS

SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF SOME IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLE DERIVATIVES

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Abstract: A number of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives having alkyl and aryl moieties attached to positions 2 and 6 of imidazo[2,1-*b*][1,3,4]thiadiazole nucleus, respectively, were prepared and characterized by IR, NMR and mass spectroscopy. Antiinflammatory activity was evaluated by carrageenan-induced rat paw edema assay. By 5th hours, all compounds demonstrated anti-inflammatory activity similar or higher than that of standard NSAID, ibuprofen.

Keywords: imidazo[2,1-*b*][1,3,4]thiadiazole, antiinflammatory activity, carrageenan

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (1). Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. Without inflammation, wounds and infections would never heal. Similarly, progressive destruction of the tissue would compromise the survival of the organism. However, chronic inflammation can also lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). It is for that reason that inflammation is normally closely regulated by the body.

Non-steroidal antiinflammatory drugs (NSAIDs) are the most commonly prescribed medications in the world. They are used for the treatment of pain, fever and inflammation, particularly arthritis (2, 3). The most prevalent side effects of the use of non-steroidal antiinflammatory drugs are the occurrence of gastrointestinal damage with gastric upset and irritation being the major problems (4, 5). The search for safer NSAIDs has intensified and continues with the failure of anticipated 'ideal' anti-inflammatory agents, the coxibs, on long-term usage (6, 7).

During recent years, there have been an intense investigations on imidazo[2,1-*b*][1,3,4]thiadiazole compounds, many of them are known to possess interesting biological properties such as anticonvulsant (8, 9), antimicrobial (10, 11), anti-inflammatory (12, 13), antitubercular (14, 15), antihypertensive (16, 17) and anticancer (18) activities. In view of the above and in continuation of our research on fused imidazo[2,1-*b*][1,3,4]thiadiazoles, we report here the anti-inflammatory activity of some 2-(4'-substituted benzyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles.

EXPERIMENTAL

Chemicals and reagents

All the chemicals used in the present study were of analytical grade and purchased from Sisco

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Research Laboratory (SRL), India. The IR spectra were recorded in KBr on a Jasco 430+ (Jasco, Japan), the ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker (400 MHz) (Bruker, Germany) aparatus, and *J* values are reported in Hertz. The melting points are uncorrected. Silica gel plates were used for the TLC by using $CHCl_3$: MeOH (9:1, v/v) mobile phase.

General procedure for the preparation of 2-amino-5-aralkyl-1,3,4-thiadiazole (2a–c)

The mixture of substituted/phenyl acetic acid **1** (0.1 M) and thiosemicarbazide (0.15 M) was added slowly to the round bottom flask containing concentrated H_2SO_4 (30 mL) with constant stirring, in ice bath. After complete addition, ice bath was replaced by water bath and slowly heated to 70–80^{o}C and maintained at that temperature for 7 h. After cooling to room temperature, the contents of reaction mixture were poured into ice water and made basic with ammonia, precipitate was filtered, washed with water and recrystallized from ethanol.

2-Amino-5-benzyl-1,3,4-thiadiazole (**2a**) (19)

Yield: 55%, m.p. 201-203^{o}C. IR (cm^{-1}): 3021, 2936, 1520, 1465, 1350, 1300, 1172, 1095, 1010; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.14 (s, 2H, -CH_2-), 7.12 (s, -NH_2, 2H), 7.23–7.34 (m, 5H). MS EI (m/z): 192.00 (M+1).

2-Amino-5-(4-chlorobenzyl)-1,3,4-thiadiazole (**2b**) (20)

Yield: 55%, m.p. 181-182^{o}C. IR (cm^{-1}): 3262, 3100, 2971, 2915, 1698, 1519, 1491, 1332, 1091, 1016; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.30 (s, 2H, -CH_2-), 7.06 (s, 2H, -NH_2), 7.55 (d, *J* = 8 Hz, 2H), 8.20 (d, *J* = 8 Hz, 2H). MS EI (m/z): 226.10 (M+1).

2-Amino-5-(4-methylbenzyl)-1,3,4-thiadiazole (**2c**) (20)

Yield: 52 %, m.p. 208-212^{o}C. IR (cm^{-1}): 3396, 3270, 3126, 2922, 1605, 1516, 1430, 1342, 1147, 1048; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 4.08 (s, 2H. -CH_2-), 7.03 (s, 2H, -NH_2), 7.14 (s, 4H, arom.).

General method for synthesis of 2-aralkyl-6-arylimidazo[2,1-*b*][1,3,4] thiadiazole (3a-3l)

A mixture of 2-amino-5-aralkyl-1,3,4-thiadiazole **2** (0.02 M) and appropriate phenacyl bromide (0.02 M) in ethyl alcohol (50 mL) was refluxed on water bath for 10-12 h. An excess of solvent was removed under reduced pressure and the solid hydrobromide that separated was filtered, washed with cold ethanol and dried. Neutralization of the above hydrobromide salts were done with cold aqueous solution of sodium carbonate (pH 7) to get corresponding bases. All free bases were purified by recrystallization from ethyl alcohol.

2-Benzyl-6-(4-chlorophenyl)imidazo[2,1-*b*][1,3,4] thiadiazole (**3a**) (21)

Yield: 45%, m.p. 163-165^{o}C. IR (cm^{-1}): 3127, 3061, 3032, 2917, 2848, 1523, 1256, 1027; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.44 (s, 2H, -CH_2-), 7.23–7.49 (m, 7H, ar), 7.82 (s, 1H, ar), 8.73 (s, 1H, im). MS (m/z): 326.10 (M). Analysis: calcd. for $C_{17}H_{12}ClN_3S$: C 62.67; H 3.71; N 12.90%; found: C 62.45; H 3.65; N 12.98%. R_f: 0.78.

2-Benzyl-6-(4-nitrophenyl)imidazo[2,1-*b*][1,3,4] thiadiazole (**3b**) (21)

Yield: 55%, m.p. 219-222^{o}C. IR (cm^{-1}): 3132, 3074, 2931, 2830, 1600, 1504, 1469, 1339, 1029; ^{1}H NMR (400 MHz, DMSO-d_6, δ. ppm): 4.46 (s, 2H, -CH_2-), 7.29–7.42 (m, 5H), 8.10 (d, *J* = 8 Hz, 2H), 8.27 (d, *J* = 8 Hz, 2H), 8.92 (s, 1H, im). MS (m/z): 337.00 (M+1). Analysis: calcd. for $C_{17}H_{12}N_4SO_2$: C 60.70; H 3.60; N 16.66%; found: C: 60.15; H: 3.49; N: 16.94%. R_f: 0.63.

2-Benzyl-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3c**) (21)

Yield: 48%, m.p. 160-162^{o}C. IR (cm^{-1}): 3134, 3058, 3033, 2973, 2864, 1524, 1470, 1232, 1177, 1092; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.30 (s, 3H, -CH_3), 4.43 (s, 2H, -CH_2-), 7.20 (d, *J* = 8 Hz, 2H), 7.29–7.41 (m, 5H), 7.73 (d, *J* = 8 Hz, 2H), 8.55 (s, 1H, im). MS (m/z): 306.00 (M+1). Analysis: calcd. for $C_{18}H_{15}N_3S$: C 70.79; H 4.95; N 13.76%; found: C 70.85; H 4.52; N 13.91%. R_f: 0.72.

2-Benzyl-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3d**) (21)

Yield: 51%, m.p. 180-182^{o}C. IR (cm^{-1}): 3133, 3062, 2960, 2910, 1611, 1522, 1488, 1430, 1244; ^{1}H NMR (400 MHz, DMSO-d_6, δ. ppm): 3.84 (s, 3H, -OCH_3), 4.33 (s, 2H, -CH_2-), 6.97 (d, *J* = 8 Hz, 2H), 7.31-7.41 (m, 5H), 7.74 (d, *J* = 8 Hz, 2H), 7.88 (s, 1H, im). MS (m/z): 322.10 (M+1). Analysis: calcd. for $C_{18}H_{15}N_3OS$: C 67.27; H 4.70; N 13.07%; found: C 66.98; H 4.59; N 13.25%. R_f: 0.68.

2-(4-Chlorobenzyl)-6-(4-chlorophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3e**) (21)

Yield: 52%, m.p. 175-178^{o}C. IR (cm^{-1}): 3147, 3057, 2927, 2861, 1528, 1476, 1403, 1092; ^{1}H NMR

(400 MHz, DMSO-d_6, δ, ppm): 4.27 (s, 2H, -CH_2-), 7.27 (d, *J* = 8 Hz, 2H), 7.35–7.38 (dd, *J* = 8, 8 Hz, 4H), 7.72 (d, *J* = 8 Hz, 2H), 7.94 (s, 1H, im). MS (m/z): 360.00 (M). Analysis: calcd. for $C_{17}H_{11}Cl_2N_3S$: C 56.68; H 3.08; N 11.66%; found: C 56.75; H 3.01; N 11.71%. R_f: 0.73.

2-(4-Chlorobenzyl)-6-(4-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3f**) (21)

Yield: 55%, m.p. 195-198°C. IR (cm^{-1}): 3130, 2925, 2832, 1597, 1504, 1414, 1338, 1266, 1098; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.47 (s, 2H, -CH_2-), 7.44 (m, 4H), 8.09 (d, *J* = 8 Hz, 2H), 8.26 (d, *J* = 8 Hz, 2H), 8.91 (s, 1H, im). MS (m/z): 369.00 (M-2). Analysis: calcd. for $C_{17}H_{11}ClO_2N_4S$: C 55.06; H 2.99; N 15.11%; found: C 54.98; H 3.01; N 15.19%. R_f: 0.67.

2-(4-Chlorobenzyl)-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3g**) (21)

Yield: 50%, m.p. 178-181°C. IR (cm^{-1}): 3143, 3055, 3021, 2961, 2924, 2865, 1596, 1535, 1461, 1290, 1935; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.37 (s, 3H, -CH_3), 4.26 (s, 2H, -CH_2-), 7.22 (d, *J* = 8 Hz. 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 8 Hz, 2H), 7.92 (s, 1H, im). MS (m/z): 340.00 (M). Analysis: calcd. for $C_{18}H_{14}ClN_3S$: C 63.62; H 4.15; N 12.36%; found: C 63.75; H 4.01; N 12.41%. R_f: 0.69.

2-(4-Chlorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3h**) (21)

Yield: 60%, m.p. 174-176°C. IR (cm^{-1}): 3146, 3040, 2939, 2842, 1609, 1537, 1482, 1252, 1025; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.84 (s, 3H, -OCH_3), 4.96 (s, 2H, -CH_2-), 6.96 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 2H), 7.88 (s, 1H, im). MS (m/z): 356.00 (M). Analysis: calcd. for $C_{18}H_{14}ClN_3OS$: C 68.03; H 5.11; N 12.53%; found: C 68.15; H 5.05; N 12.75%. R_f: 0.71.

2-(4-Methylbenzyl)-6-(4-chlorophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole (**3i**)

Yield: 50%, m.p. 226-228°C. IR (cm^{-1}): 3124, 2909, 1525, 1470; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.83 (s, 3H, -CH_3), 4.37 (s, 2H, -CH_2-), 7.18 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 8.66 (s, 1H, im). MS (m/z): 362.10 (M+Na). Analysis: calcd. for $C_{18}H_{14}ClN_3S$: C 63.62; H 4.15; N 12.36%; found: C 63.55; H 4.10; N 12.41%. R_f: 0.73.

2-(4-Methylbenzyl)-6-(4-nitrophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole (**3j**)

Yield: 45%, m.p. 170-175°C. IR (cm^{-1}): 3125, 2867, 1598, 1414; Analysis: calcd. for $C_{18}H_{14}N_4O_2S$: C 61.70; H 4.03; N 15.99%; found: C 61.59; H 3.99; N 16.07%. R_f: 0.72.

Table 1. Inhibition of paw edema in rats by synthesized compounds.

Compd.	Inhibition (%)	
	At 3rd h	At 5th h
3a	26.34 ± 0.89	78.87 ± 3.80***b
3b	14.87 ± 4.64	63.10 ± 3.24
3c	49.99 ± 0.00***a	34.17 ± 5.58‡
3d	41.65 ± 5.27 *a	75.00 ± 3.73
3e	37.50 ± 12.50	83.33 ± 0.00
3f	17.49 ± 2.50	55.00 ± 3.42
3g	30.35 ± 1.44	52.38 ± 6.82
3h	20.83 ± 2.38	59.45 ± 5.60
3i	19.99 ± 2.23	56.11 ± 3.89
3j	22.21 ± 4.65	63.89 ± 9.51
3k	36.66 ± 6.01	51.11 ± 4.36†
3l	36.66 ± 6.01	51.11 ± 4.36†
Ibuprofen	14.16 ± 1.89	71.67 ± 3.80

Values are the mean ± SEM, n = 6. ***b - $p < 0.01$, when compared to ibuprofen at 5th hour. ***a - $p < 0.001$, when compared to ibuprofen at 3rd hour. *a - $p < 0.05$, when compared to ibuprofen at 3rd hour. ‡ - $p < 0.01$, when compared to ibuprofen at 5th hour. † - $p < 0.05$, when compared to ibuprofen at 5th hour.

2-(4-Methylbenzyl)-6-(4-methylphenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole (3k)

Yield: 52%, m.p. 180-182°C. IR (cm^{-1}): 3118, 2868, 1587, 1460; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 4.37 (s, 2H, -CH_2-), 7.19 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 2H), 8.54 (s, 1H, -CH-). MS (m/z): Analysis: calcd. for $C_{19}H_{17}N_3S$: C 71.44; H 5.36; N 13.15%; found: C 71.06; H 5.25; N 13.21%. R_f: 0.65.

2-(4-Methylbenzyl)-6-(4-methoxyphenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole (3l)

Yield: 55%, m.p. 138-140°C. IR (cm^{-1}): 3141, 2936, 1603, 1477; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, -CH_3), 3.76 (s, 3H, -OCH_3), 4.36 (s, 2H, -CH_2-), 6.94-7.78 (m, 8H, ar), 8.48 (s, 1H, -CH-). MS (m/z): 358.10 (M+Na). Analysis: calcd. for $C_{19}H_{17}N_3OS$: C 68.03; H 5.11; N 12.53%; found: C 67.95; H 5.01; N 12.61%. R_f: 0.68.

Antiinflammatory activity

Acute antiinflammatory activity of selected compounds was evaluated in Wistar albino rats, after taking clearance for animal experimentation from Institutional Animal Ethics Committee of KLE University's College of Pharmacy, Bangalore. Naive animals (200-250 g, either sex) were challenged with 0.5 mL of 1% carrageenan [intraplantar injection into right paw] (22), after one hour of oral administration of newly synthesized compounds in the dose of 100 mg/kg. Simultaneously, a group of animals was treated with ibuprofen (100 mg/kg body weight) for comparative purposes. Edema, a cardinal sign of inflammation, was measured at regular intervals (3rd, 5th h, post challenge) by mercury displacement method using plethysmograph (23). Percentage inhibition of edema in various groups of animals treated with newly synthesized compounds and ibuprofen are tabulated in Table 1.

Statistical analysis

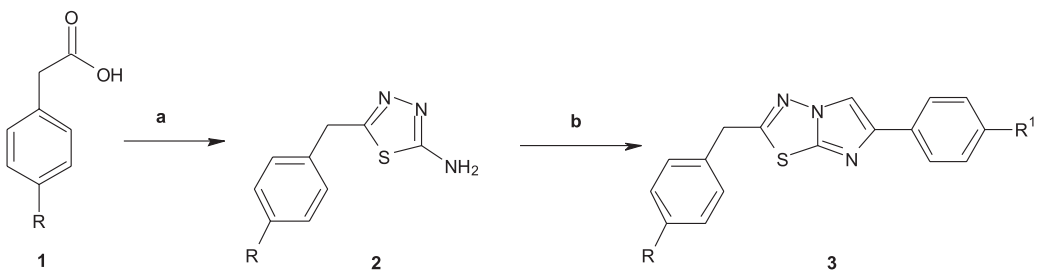
Statistical significance for inhibition of edema between various groups was determined using one way ANOVA followed by *post-hoc* Newman-Keuls multiple comparison. Values $p < 0.05$ was considered significant.

RESULT AND DISCUSSION

Chemistry

We have synthesized a series of 12 derivatives of imidazo[2,1-*b*][1,3,4]thiadiazoles containing aralkyl group at 2nd position by reacting 2-amino-5-aralkyl-1,3,4-thiadiazoles **1** with 4-substituted phenacyl bromide (Scheme 1). Structures of the synthesized compounds were established on the basis of IR, ^{1}H NMR and MS analysis. All synthesized compounds showed absorption bands ranging from 3141 to 3118 cm^{-1} for C-H aromatic stretching and 2936 to 2868 cm^{-1} for C-H aliphatic stretching.

In ^{1}H NMR, the presence of singlet between δ 8.66-8.48 ppm for imidazole proton (C5-H) confirmed the cyclization of compound **2** with 4-substi-



R = H (**a**); Cl (**b**); CH_3 (**c**)

R = H, R^1 = Cl (**a**); R = H, R^1 = NO_2 (**b**);
R = H, R^1 = CH_3 (**c**); R = H, R^1 = OCH_3 (**d**)
R = Cl, R^1 = Cl (**e**); R = Cl, R^1 = NO_2 (**f**);
R = Cl, R^1 = CH_3 (**g**); R = Cl, R^1 = OCH_3 (**h**);
R = CH_3, R^1 = Cl (**i**); R = CH_3, R^1 = NO_2 (**j**);
R = CH_3, R^1 = CH_3 (**k**); R = CH_3, R^1 = OCH_3 (**l**)

Scheme 1. Synthesis of compounds **3a**-**3l**. Reagents and conditions: a - thiosemicarbazide, H_2SO_4, NH_3; b - 4-substituted phenacyl bromides, ethanol, reflux, Na_2CO_3

tuted phenacyl bromide. Compounds (**3a-3l**) showed prominent signals for aromatic protons around δ 7.86-6.94 ppm. Methylene proton at C_2 appeared between δ 4.37-4.36 ppm for synthesized derivatives (**3a-3l**). Compounds **3a**, **3l**, **3k** and **3j** showed singlet between δ 2.83-2.28 ppm for the presence of methyl proton on phenyl ring. Compound **3l** showed a singlet at δ 3.76 ppm for the presence of -OCH_3 at the phenyl ring.

Antiinflammatory activity

Acute antiinflammatory activities of newly synthesized compounds (**3a-3l**) were evaluated by carrageenan induced paw edema of rat at the dose of 100 mg/kg (p. o.) and expressed as percentage of inhibition of edema, after 3 and 5 h as shown in Table 1. By 3rd hour, percentage of edema inhibition ranged between 14 and 47% and by 5th hour, between 34 and 78%, suggestive of prolonged anti-inflammatory activity.

By 3rd hour, all compounds demonstrated anti-inflammatory activity similar or higher than that of standard NSAID, ibuprofen. However, **3c** and **3d** demonstrated significantly ($p < 0.001$ and $p < 0.05$, respectively) higher activity than ibuprofen. Even after 5 hours, all compounds continue to demonstrate significant antiinflammatory activity (except for **3c** and **3k** and **3l**) where the activity was significantly reduced compared to ibuprofen. Animals treated with **3a** recorded a higher and significant ($p < 0.001$) antiinflammatory activity than ibuprofen by 3rd hour of post-carrageenan challenge.

Structure activity relation

Imidazo[2,1-*b*][1,3,4]thiadiazole derivatives with substituents like Cl, NO_2, CH_3 and OCH_3 at 4th position of phenyl group did not gave any improvement in antiinflammatory activity in comparison to ibuprofen by 3rd hour treatment except derivatives **3b**, **3f** and **3i**. However, when substitutions were made at 4th position of both benzyl and phenyl groups of imidazo[2,1-*b*][1,3,4] thiadiazole, by electron withdrawing and electron donating groups, compounds demonstrated significant antiinflammatory activity in the dose of 100 mg/kg body weight.

CONCLUSION

We have synthesized 12 derivatives of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles by reacting 2-amino-5-aralkyl-1,3,4-thiadiazole with various phenacyl bromides in good yields. Among the tested compounds, compound **3c** with the 4-methyl substitution in the phenyl ring at 6 position of the imidazo[2,1-*b*][1,3,4] thiadiazole ring demonstrated 34% edema inhibition after 5th hour of carrageenan challenge. Further studies are required to establish its exact mechanism of action.

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