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RESEARCH ARTICLE

Synthesis, Characterization and Biological Evaluation of Some Thiazole Derivatives Bearing 2,2,Difluorobenzo[d][1,3]Dioxole Nucleus

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ABSTRACT

A series of thiazole derivatives have been synthesized and tested for in vitro antibacterial and antifungal activity on different microorganisms. Synthesis of 2,2-difluoro-N'-(4-substitutedphenylthiazol-2-yl)[d][1,3]dioxole-5-carbohydrazide have been carried out from 2-[(2,2-difluoro-1,3-benzodioxol-5-yl)carbonyl]hydrazine carbothioamide and substituted phenacyl bromide in dioxane. The structure and purity of the original compounds were confirmed by IR, LCMS, NMR and elemental analysis.

KEYWORDS

2-[(2,2-difluoro-1,3-benzodioxol-5-yl)carbonyl]hydrazine carbothioamide, Phenacyl bromide, substituted thiosemicarbazide

INTRODUCTION

Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring. Thiazole and related compounds are called 1, 3-azoles (nitrogen and one other heteroatom in a five-membered ring). They are isomeric with the 1, 2-azoles, the nitrogen and sulfur compound being called isothiazole.

Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug).

It has been noticed continuously over the years that interesting biological activities[1-2] were associated with thiazole derivatives.

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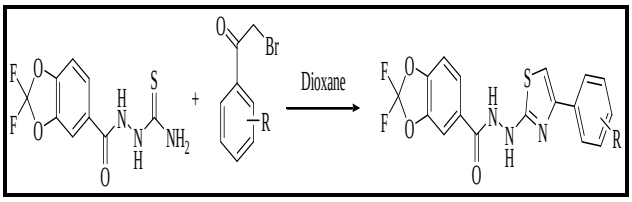
Recently the applications of thiazoles were found in drug development for the treatment of allergies[3], hypertension[4], inflammation[5], schizophrenia[6], bacterial[7], HIV infections[8], hypnotics[9] and more recently for the treatment of pain[10], as fibrinogen receptor antagonists with antithrombotic activity[11] and as new inhibitors of bacterial DNA gyrase B.[12] A brief review of thiazoles associated with large number of biological activities is presented below.

Reaction Scheme



EXPERIMENTAL

General method for the preparation of 2,2-difluoro-N'-(4-(substitutedphenyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide.

To the solution of 2-[(2,2-difluoro-1,3-benzodioxol-5-yl)carbonyl]hydrazine carbothioamide (1 mmol) in 10 mL of 1,4-Dioxane was added substituted Phenacyl bromide (1 mmol). The reaction mixture was stirred under warming up to reflux temperature for 6 hours. Cool the reaction mixture up to ambient temperature. Insoluble solid gradually was generated. Then filter the residue and wash with dioxane. After drying desired compound was afforded as a crystalline solid.

2-2-difluoro-N'-(4-(3,4-difluorophenyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide (6a).

Yield: 92%; mp 198-201^{o}C; HR-MS (ESI): calcd for $C_{17}H_9F_4N_3O_3S$ (M^++H): 411.03; C, 49.64; H, 2.21; F, 18.48; N, 10.22; O, 11.67; S, 7.80; Found: C, 49.60; H, 2.19; F, 18.53; N, 10.26; O, 11.78; S, 7.64; IR (cm^{-1}): 3218 (N-H), 2674 (C-S), 1632 (C=O Amide), 1481 (C=C), 1376 (C-H), 1270 (C-N), 1248 (C-N), 1186 (C-O), 1101 (C-F), 753, 678 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 10.99 (s, 1H), 9.83 (s, 1H), 7.90 (s, 1H), 7.86-7.83 (m, 2H), 7.68 (s, 1H), 7.59 (d, J= 8.4Hz, 1H), 7.49-7.42 (m, 2H).

2,2-difluoro-N'-(4-phenylthiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide (6b). Yield: 83%; mp 257-261^{o}C; HR-MS (ESI): calcd for $C_{17}H_{11}F_2N_3O_3S$ (M^++H): 375.05; C, 54.40; H, 2.95; F, 10.12; N, 11.19; O, 12.79; S, 8.54; Found: C, 54.28; H, 2.81; F, 10.32; N, 11.29; O, 12.58; S, 8.72; IR (cm^{-1}): 3194 (N-H), 2672 (C-S), 2838 (C-H), 1612 (C=O Amide), 1487 (C=C), 1378 (C-H), 1281 (C-N), 1238 (C-N) 1171 (C-O), 1102 (C-F), 762, 699 (mono), 676 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.00 (s, 1H), 9.84 (s, 1H), 7.91 (s, 1H), 7.83 (m, 2H), 7.58 (d, J= 8.4Hz, 1H), 7.43-7.31 (m, 5H).

N'-(4-(4-bromophenyl)thiazol-2-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (6c).

Yield: 93%; mp 243-247^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}BrF_2N_3O_3S$ (M^++H): 452.96; C, 44.95; H, 2.22; Br, 17.59; F, 8.36; N, 9.25; O, 10.57; S, 7.06; Found: C, 44.83; H, 2.41; Br, 17.47; F, 8.51; N, 9.11; O, 10.51; S, 7.16; IR (cm^{-1}): 3214 (N-H), 2632 (C-S), 1623 (C=O Amide), 1491 (C=C), 1368 (C-H), 1284 (C-N), 1243 (C-N) 1175 (C-O), 1113 (C-F), 835 (para), 691 (C-S), 624 (C-Br); ^{1}H NMR (400 MHz, DMSO): δ = 11.03 (s, 1H), 9.85 (s, 1H), 7.92 (s, 1H), 7.89 (dd, J= 7.6Hz, 2H), 7.85 (m, 2H), 7.60 (d, J= 8.4Hz, 1H), 7.37 (dd, J= 8Hz, 2H).

N'-(4-(3,5-bis(trifluoromethyl)phenyl)thiazol-2-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (6d).

Yield: 85%; mp 266^{o}C; HR-MS (ESI): calcd for $C_{19}H_9F_8N_3O_3S$ (M^++H): 511.02; C, 44.63; H, 1.77; F, 29.72; N, 8.22; O, 9.39; S, 6.27; Found: C, 44.52; H, 1.64; F, 29.70; N, 8.37; O, 9.43; S, 6.34; IR (cm^{-1}): 3168 (N-H), 2694 (C-S), 2802 (C-H), 1616 (C=O Amide), 1485 (C=C), 1382 (C-H), 1266 (C-N), 1249 (C-N) 1180 (C-O), 1131 (C-F), 900 (meta), 754, 684 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.04 (s, 1H), 9.94 (s, 1H), 8.48 (s, 1H), 8.00 (s, 1H), 7.90 (s, 1H), 7.84 (d, J= 8 Hz, 1H), 7.60 (d, J= 8.4Hz, 1H), 7.12-6.73 (b, 2H).

2,2-difluoro-N'-(4-p-tolylthiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide (6e). Yield: 92%; mp 181-191^{o}C; HR-MS (ESI): calcd for $C_{18}H_{13}F_2N_3O_3S$ (M^++H): 389.07; C, 55.52; H, 3.37; F, 9.76; N, 10.79; O, 12.33; S, 8.23; Found: C, 55.67; H, 3.24; F, 9.88; N, 10.61; O, 12.48; S, 8.12; IR (cm^{-1}): 3224 (N-H), 2681 (C-S), 1627 (C=O Amide), 1489 (C=C), 1382 (C-H), 1283 (C-N), 1250 (C-N) 1178 (C-O), 1109 (C-F), 829 (para), 754, 689 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 10.99 (s, 1H), 9.84 (s, 1H), 7.89 (s, 1H), 7.83 (m, 2H), 7.58 (d, J= 8Hz, 1H), 7.42 (dd, J= 8Hz, 2H), 7.12 (dd, J= 8.4Hz, 2H), 2.30 (s, 3H).

N'-(4-(3-bromophenyl)thiazol-2-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (6f).

Yield: 93%; mp 232-234^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}BrF_2N_3O_3S$ (M^++H): 452.96; C, 44.95; H, 2.22; Br, 17.59; F, 8.36; N, 9.25; O, 10.57; S, 7.06; Found: C, 44.78; H, 2.42; Br, 17.37; F, 8.53; N, 9.46; O, 10.28; S, 7.16; IR

(cm^{-1}): 3185 (N-H), 2819 (C-H), 2671 (C-S), 1619 (C=O Amide), 1478 (C=C), 1391 (C-H), 1268 (C-N), 1237 (C-N) 1168 (C-O), 1103 (C-F), 900 (meta), 754, 678 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.02 (s, 1H), 9.84 (s, 1H), 7.91 (s, 1H), 7.83 (m, 2H), 7.57 (d, J= 8.4Hz, 1H), 7.65 (s, 1H), 7.46-7.34 (m, 3H).

N'-(4-(2-chlorophenyl)thiazol-2-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (6g).

Yield: 91%; mp 228-231^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}ClF_2N_3O_3S$ (M^++H): 409.01; C, 49.83; H, 2.46; Cl, 8.65; F, 9.27; N, 10.25; O, 11.71; S, 7.82; Found: C, 49.88; H, 2.35; Cl, 8.41; F, 9.58; N, 10.33; O, 11.67; S, 7.78; IR (cm^{-1}): 3212 (N-H), 2614 (C-S), 1621 (C=O Amide), 1492 (C=C), 1389 (C-H), 1274 (C-N), 1237 (C-N) 1178 (C-O), 1098 (C-F), 895 (meta), 758 (ortho), 684 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 10.98 (s, 1H), 9.83 (s, 1H), 7.89 (s, 1H), 7.82 (m, 2H), 7.58 (d, J= 8.4Hz, 1H), 7.21-7016 (m, 4H).

2,2-difluoro-N'-(4-(4-fluorophenyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide (6h).

Yield: 88%; mp 253^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}F_3N_3O_3S$ (M^++H): 393.04; C, 51.91; H, 2.56; F, 14.49; N, 10.68; O, 12.20; S, 8.15; Found: C, 51.78; H, 2.64; F, 14.53; N, 10.46; O, 12.39; S, 8.20; IR (cm^{-1}): 3228 (N-H), 2685 (C-S), 1621 (C=O Amide), 1492 (C=C), 1381 (C-H), 1286 (C-N), 1253 (C-N), 1175 (C-O), 1108 (C-F), 823 (para), 690 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.03 (s, 1H), 9.82 (s, 1H), 7.92 (d, J = 1.6Hz, 1H), 7.83-7.89 (m, 2H), 7.61 (d, J= 8.4Hz, 1H), 7.27-7.21 (m, 4H), 7.10 (s, 1H).

N'-(4-(2-bromophenyl)thiazol-2-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (6i).

Yield: 90%; mp 278-281^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}BrF_2N_3O_3S$ (M^++H): 452.96; C, 44.95; H, 2.22; Br, 17.59; F, 8.36; N, 9.25; O, 10.57; S, 7.06; Found: C, 44.82; H, 2.41; Br, 17.39; F, 8.58; N, 9.25; O, 10.42; S, 7.13; IR (cm^{-1}): 3209 (N-H aromatic ring), 2628 (C-S), 1627 (C=O Amide), 1483 (C=C), 1381 (C-H), 1278 (C-N), 1238 (C-N) 1173 (C-O), 1092 (C-F), 824 (meta), 762 (ortho), 672 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.04 (s, 1H), 9.85 (s, 1H), 7.92 (s, 1H), 7.84 (m, 2H), 7.62 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.52 (d, J= 8.4Hz, 1H), 7.43 (m, 2H).

2,2-difluoro-N'-(4-(4-nitrophenyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carbohydrazide (6j).

Yield: 87%; mp 182-183^{o}C; HR-MS (ESI): calcd for $C_{17}H_{10}F_2N_4O_5S$ (M^++H): 420.03; C, 48.57; H, 2.40; F, 9.04; N, 13.33; O, 19.03; S, 7.63; Found: C, 48.32; H, 2.26; F, 9.48; N, 13.39; O, 19.12; S, 7.43; IR (cm^{-1}): 3211 (N-H), 2674 (C-S), 1628 (C=O Amide), 1478 (C=C), 1392 (C-H), 1271 (C-N), 1239 (C-N) 1171 (C-O), 1097 (C-F), 838 (para), 761, 692 (C-S); ^{1}H NMR (400 MHz, DMSO): δ = 11.06 (s, 1H), 9.86 (s, 1H), 8.63 (dd, J= 8Hz, 2H), 8.32 (dd, J= 8Hz, 2H), 7.93 (s, 1H), 7.85 (m, 2H), 7.61 (d, J= 8.4Hz, 1H).

CONCLUSION

In summary, on the basis of various literature survey thiazole derivatives possessing a wide spectrum of biological activities like antibacterial, anti-tuberculosis, anticancer, anti-inflammatory etc. Series of compounds were synthesized by using same approach. We have demonstrated a simple route for the synthesis of thiazole via cyclocondensation reaction of substituted thiosemicarbazide and different substituted phenacyl bromide using Dioxane as solvent. This protocol is general and provides thiazoles in good to excellent yields depending on the reactivity of phenasylbromide. Thiazoles synthesize by this method is pure no need further purification. Thus, the present synthesis of thiazoles will serve as an exclusive method of preparative importance for this class of compounds.

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