Facile synthesis of new 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones

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Facile synthesis of new 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones

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ABSTRACT

The reaction of 2-bromo-1,4-naphthoquinone with 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols in ethanol at 50 °C gave the corresponding 2-[(4-amino-5-aryl-4*H*-1,2,4-triazol-3-yl)thio]naphthalene-1,4-diones. Their treatment with EtOH/HCl under reflux conditions produced 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones through intramolecular cyclization.

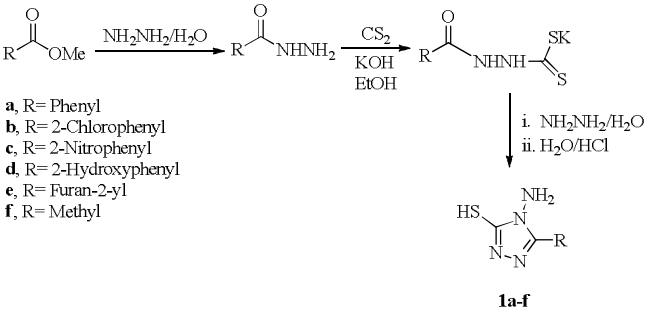
1,2,4-Triazole derivatives are an important class of heterocyclic compounds with agricultural, pharmacological and biological activities,[1-3] such as anticonvulsant,[4] anti-inflammatory[5] and antimicrobial.[6,7]

Naphthoquinones are also important compounds due to their biological and pharmaceuitical activites,[8] including antibacterial,[9] antifungal,[10] anti-inflammatory,[11] antileishmanial,[12] antitumor,[13] and molluscicidal.[14,15]

It continuation of our studies on the synthesis of bi-, tri- and tetracyclic heterocycles,[16-27] we have recently reported[28] the synthesis of naphtho[2',3':4,5]imidazo[2,1-*b*][1,3]thiazol-5,10-dione and naphtho[2',3':4,5]imidazo[2,1-*b*][1,3]benzothiazole-7,12-dione by the reaction of 2,3-dibromo-1,4-naphthoquinone with 2-aminothiazole and 2-aminobenzothiazole respectively.

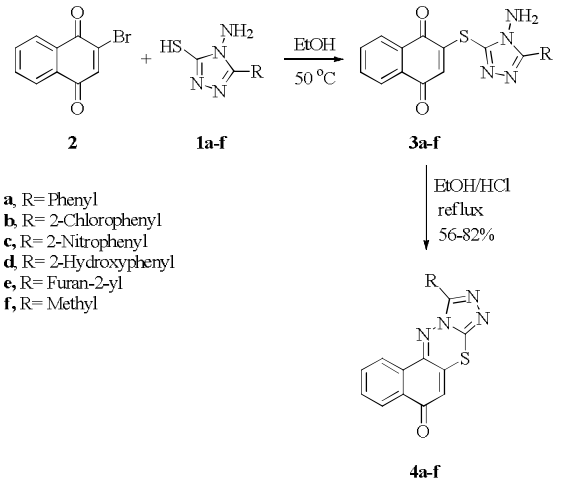
Herein we report the synthesis of new 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones **4a-f** by reaction of 2-bromo-1,4-naphthoquinone (**2**) with 4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazole-3-thiols **1a-f**.

Thus 4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazole-3-thiols **1a-f** were prepared using commercially available methyl carboxylate esters as shown in Scheme 1.[29]



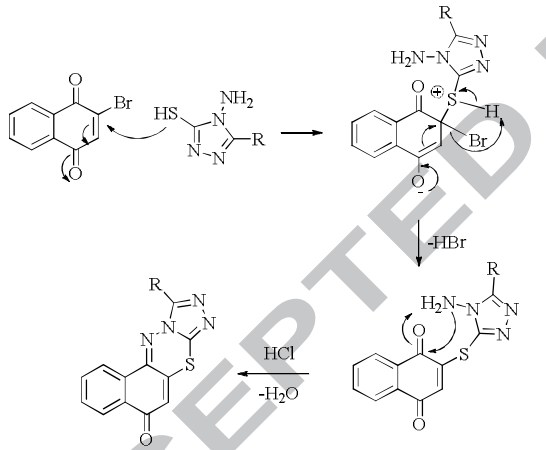
Scheme 1. Preparation of 4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazole-3-thiols **1a-f**

Reaction of 4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazole-3-thiols **1a-f** with 2-bromo-1,4-naphthoquinone (**2**) in ethanol at 50 °C gave the corresponding 2-[(4-amino-5-aryl(alkyl)4*H*-1,2,4-triazol-3-yl)thio]naphthalene-1,4-diones **3a-f**. Treatment of intermediates **3a-f** with EtOH/HCl under reflux conditions formed 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones **4a-f** (Scheme 2).



Scheme 2. Synthesis of 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones **4a-f**

The proposed mechanism involves the initial attack of the mercapto group at the bromine substituent to form the intermediates **3a-f**. This is followed by subsequent dehydration in the presence of HCl as the catalyst to produce the corresponding tetracyclic heterocycles **4a-f** via intramolecular cyclization as shown in Scheme 3.



Scheme 3. Proposed reaction mechanism for the formation of **4a-f**.

The structures of all the products were identified from their FT-IR, ^{1}H and ^{13}C NMR spectral data and by elemental analysis.

In summary, we have described the synthesis of 10-substituted derivatives of 5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-5-ones, which represents a new tetracyclic heterocyclic ring system. The procedure used in this report can be extended to the synthesis of other polycyclic heterocycles.

General procedure for synthesis of 2-[(4-amino-5-aryl(alkyl)4*H*-1,2,4-triazol-3-yl)thio]naphthalene-1,4-diones 3a-f

To a solution of 2-bromo-1,4-naphthoquinone (**2**) (1 mmol) in $CHCl_3$ (5 mL) was added a solution of 4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazole-3-thiol (**1**) (1 mmol) in absolute EtOH (5 mL). The mixture was stirred at 50 °C until the reaction was complete (TLC). Removal of the solvent and recrystallization from EtOH gave the desired products as yellow needles.

General procedure for synthesis of 10-substituted-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-ones 4a-f

To a solution of 2-[(4-amino-5-aryl(alkyl)-4*H*-1,2,4-triazol-3-yl)thio]naphthalene-1,4-dione (1 mmol) in EtOH (20 mL) was added concentrated HCl (4-5 drops). The mixture was refluxed for 4 h. The mixture was left to cool to room temperature and the resulting precipitate was filtered, washed with cold EtOH and dried to give products **4a-f** as orange needles in 56-82% yields.

10-Phenyl-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4a)

Orange solid, 73%, mp 227-228 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.45 (1H, t, *J* = 3.6, Ar); 8.28 (1H, t, *J* = 6.3, Ar); 8.2 (1H, d, *J* = 3.6, Ar); 8.1 (1H, d, *J* = 2.1, Ar); 7.87-7.76 (2H, m, Ar); 7.64 (3H, t, *J* = 3.3, Ar); 6.91 (1H, s, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 179.97, 152.85, 140.76, 136.06, 133.16, 132.40, 131.76, 131.30, 131.01, 130.36, 128.90, 128.89, 126.79, 126.65, 125.13, 124.53. IR (KBr), ν, cm^{-1}: 1642, 1595, 1550, 1457, 1356, 1303 1130, 778, 691. Found, %: C, 65.59; H, 2.96; N, 17.02. $C_{18}H_{10}N_4OS$. Calcd %: C, 65.44; H, 3.05; N, 16.96.

10-(2-Chlorophenyl)-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4b)

Yellow solid, 82%, mp 156-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.16 (1H, br d, *J* = 6.9, Ar); 8.11 (1H, br d, *J* = 6.9, Ar); 8.04 (1H, d, *J* = 7.5, Ar); 7.76-7.84 (2H, m, Ar); 7.59 (1H, d, *J* = 7.8, Ar); 7.54 (1H, t, *J* = 7.8, Ar); 7.46 (1H, t, *J* = 6.9, Ar); 7.36 (1H, s, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 181.63, 181.02, 165.91, 158.69, 146.98, 134.95, 133.39, 133.14, 131.91, 131.42, 131.36, 131.16, 127.27, 127.10, 126.98, 122.29. IR (KBr), ν, cm^{-1}: 3069, 1659, 1589, 1567, 1467, 1295, 1256, 1187, 851, 770. Found, %: C, 59.33; H, 2.38; N, 15.41. $C_{18}H_9ClN_4OS$. Calcd %: C, 59.26; H, 2.49; N, 15.36.

10-(2-Nitrophenyl)-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4c)

Red solid, 64%, mp 192-193 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.01 (1H, dd, J_1 = 8.4, J_2 = 2.1, Ar); 7.97-7.80 (3H, m, Ar); 7.61 (1H, d, *J* = 7.8, Ar); 7.27 (1H, t, *J* = 7.5, Ar), 7.15 (1H, s, H-2); 6.90 (1H, d, *J* = 8.1, Ar); 6.65 (1H, t, *J* = 7.5, Ar). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 182.03, 181.36, 167.74, 155.80, 148.45, 147.34, 135.50, 134.63, 133.56, 133.77, 132.02, 131.48, 128.32, 126.99, 126.74, 116.59, 116.14, 103.92. IR (KBr), ν, cm^{-1}: 3063, 2815, 2558, 1738, 1657, 1619, 1588, 1549, 1471, 1341, 1295, 1258, 1170, 1064, 773, 697. Found, %: C, 57.55; H, 2.57; N, 18.54. $C_{18}H_9N_5O_3S$. Calcd %: C, 57.60; H, 2.42; N, 18.66.

10-(2-Hydroxyphenyl)-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4d)

Yellow solid, 70%, mp 240-242 °C, ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.33 (1H, s, exchanged by D_2O addition, OH); 8.2 (1H, d, *J* = 7.5, Ar); 8.09 (d, 1H, *J* = 7.5, Ar); 7.9 (1H, t, *J* = 8.1, Ar); 7.81 (1H, t, *J* = 7.5, Ar); 7.68 (1H, d, *J* = 7.5, Ar); 7.5 (1H, t, *J* = 7.8, Ar); 7.27 (1H, s, H-2); 7.1 (1H, d, *J* = 8.4, Ar); 7.07 (1H, t , *J* = 7.8, Ar). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 180.30, 157.05, 151.91, 140.13, 136.85, 133.64, 132.97, 132.63, 132.36, 131.68, 131.38, 131.13, 126.43,

126.28, 124.49, 119.63, 116.93, 112.20. IR (KBr), ν, cm^{-1}: 3424, 2925, 1659, 1626, 1588, 1480, 1298, 1250, 1159. Found, %: C, 62.31; H, 3.12; N, 16.21. $C_{18}H_{10}N_4O_2S$. Calcd %: C, 62.42; H, 2.91; N, 16.18.

10-(Furan-2-yl)-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4e)

Orange solid, 56%, mp 244 °C, ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.52 (1H, d, *J* = 7.8, Ar); 8.12 (1H, d, *J* = 7.5, Ar); 8.07 (1H, s, Ar); 7.94 (1H, t, *J* = 7.8, Ar); 7.86 (1H, t , *J* = 7.5, Ar); 7.50 (1H, d, *J* = 3.3, Ar); 7.25 (1H, br s, Ar); 6.85 (1H, dd, J_1 = 3.3, J_2 = 1.5, Ar). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 180.33, 146.31, 145.4, 141.07, 139.95, 137.23, 133.90, 132.86, 132.22, 131.96, 131.15, 126.50, 126.38, 125.03, 114.64, 112.93. IR (KBr), ν, cm^{-1}: 2923, 1642, 1622, 1550, 1453, 1308, 771. Found, %: C, 60.11; H, 2.40; N, 17.52. $C_{16}H_8N_4O_2S$. Calcd %: C 59.99; H, 2.52; N, 17.49.

10-Methyl-5*H*-naphtho[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-5-one (4f)

Orange solid, 67%, mp 248 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.53 (1H, d, *J* = 7.2, Ar); 8.23 (1H, d, *J* = 6.9, Ar); 7.80-7.76 (2H, m, Ar); 6.85 (1H, s, Ar); 2.78 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 179.97, 151.66, 140.19, 135.17, 132.99, 132.36, 131.62, 131.17, 130.75, 126.70, 126.54, 124.32. IR (KBr), ν, cm^{-1}: 2923, 2854, 1641, 1594, 1548, 1459, 1357, 1307, 1131, 779. Found, %: C, 58.36; H, 2.93; N, 20.94. $C_{13}H_8N_4OS$. Calcd %: C, 58.20; H, 3.01; N, 20.88.

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Graphical Abstract

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