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Note

Synthesis and biological activities of some 2-chloro-6/8-substituted-3-(3-alkyl/ aryl-5,6-dihydro-*s*-triazolo-[3,4-*b*] [1,3,4]thiadiazol-6-yl)quinolines

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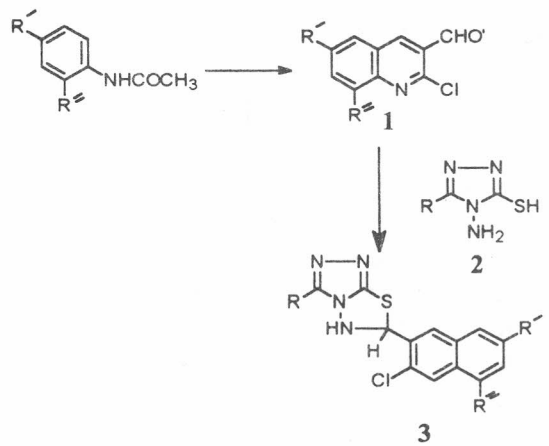
Various 3-substituted-4-amino-5-mercapto-1, 2, 4-triazoles **2** when condensed with substituted 2-chloro-3-formylquinolines **1** in DMF or DMF/K_2CO_3 give 2-chloro-6/8-substituted-3-(3-alkyl/aryl-5, 6-dihydro-*s*-triazolo[3,4-*b*][1, 3, 4]thiadiazol-6-yl)quinolines **3**. The quinolines **3** have been assessed for their antiinflammatory, antibacterial and antifungal activities.

In recent years, the chemistry of quinolines[1-3] and their derivatives has gained increasing attention, particularly because substituted quinolines are associated with immense biological activities[4-9]. Like-wise, a triazolo-thiadiazole system is also found to be associated with wide range of biological activities[10-14]. As a part of our programme on the synthesis of potentially bioactive heterocyclic systems[15-17], we report herein the synthesis of 2-chloro-6/8-substituted-3-(3-alkyl/aryl-5, 6-dihydro-*s*-triazolo[3,4-*b*][1,3,4]-thiadiazol-6-yl)quinolines **3** incorporating two biologically active moieties in a single molecule. The title compounds have been evaluated for their antiinflammatory, antibacterial and antifungal activities.

It has been reported[18] that the reaction of *o*-aminothiophenol and 2-chloro-3-formyl-6-methylquinoline when carried out in DMF containing K_2CO_3 proceeds with the displacement of chlorine atom giving quino[2, 3-*b*][1,5]benzothiazepines, while in only DMF it gives 3-(benzothiazolin-2-yl)-2-chloro-6-methylquinoline retaining the chlorine atom. Mercaptoaminotriazole is analogous to *o*-aminothiophenol and based on our interest in exploring the utility of mercaptoaminotriazole as an important synthon in the synthesis of heterocyclic systems, we have carried out the reaction of mercaptoaminotriazole with 2-chloro-3-formyl-6/8-substituted quinolines in both the conditions, DMF and DMF/K_2CO_3. It has been found that the same products, 2-chloro-6/8-substituted-3-(3-alkyl/aryl-5, 6-dihydro-*s*-triazolo[3,4-*b*] [1,3,4]thiadiazol-6-yl)quinolines **3**, are obtained when the reaction is carried out in DMF or DMF/K_2CO_3.



3a; R= $CH_2C_6H_5$,	R′= OMe,	R″= H
3b; R=4- $OMeC_6H_4$,	R′= OMe,	R″= H
3c; R=2-$CH_3C_6H_4$,	R′= OMe,	R″= H
3d; R= CH_3,	R′= OMe,	R″= H
3e; R= C_2H_5,	R′= OMe,	R″= H
3f; R= C_3H_7,	R′= OMe,	R″= H
3g; R= $CH_2C_6H_5$,	R′= CH_3,	R″= H
3h; R= 4-$OMeC_6H_4$	R′= CH_3,	R″= H
3i; R= 2-$CH_3C_6H_4$	R′= CH_3,	R″= H
3j; R= CH_3	R′= CH_3,	R″= H
3k; R= C_2H_5	R′= CH_3,	R″= H
3l; R= C_3H_7	R′= CH_3,	R″= H
3m; R= $CH_2C_6H_5$	R′= CH_3,	R″= H
3n; R= 4-$OMeC_6H_4$	R′= CH_3,	R″= H
3o; R= 2-$CH_3C_6H_4$	R′= CH_3,	R″= H
3p; R= CH_3	R′= CH_3,	R″= H
3q; R= C_2H_5	R′= CH_3,	R″= H
3r; R= C_3H_7	R′= CH_3,	R″= H
3s; R= $CH_2C_6H_5$	R′= R″= H	
3t; R= 4-$OMeC_6H_4$	R′= R″= H	
3u; R= 2-$CH_3C_6H_4$	R′= R″= H	
3v; R= CH_3	R′= R″= H	
3w; R= C_2H_5	R′= R″= H	
3x; R= C_3H_7	R′= R″= H	

The required synthons substituted 2-chloro-3-formylquinolines[19] **1**, 3-substituted-4-amino-5-mercapto-1, 2, 4-triazoles[20,21] **2** were prepared by literature methods.

The structural assignments of **3** are based on IR and ^{1}H NMR data. The IR spectra of **3a-z** showed sharp bands near 1620 and 3250-3375 cm^{-1} due to C=N and NH groups respectively. The bands that appeared at 3210, 3150 (NH_2), 1130 cm^{-1} (C=S) and 1690 cm^{-1} (C=O) for the starting triazoles **2** and aldehydes **1** respectively were absent in the newly formed compounds **3a-z**. The ^{1}H NMR spectra of **3a-z** exhibited broad singlets at δ4.9-5.4, exchangeable with D_2O, due to –N*H*–C*H* proton whereas, –NH–C*H* protons appeared as a singlet at δ6.30-6.52. The aromatic protons appeared as a multiplet at δ7.20-8.40 and as a singlet at δ8.85-9.1. The ^{1}H NMR spectra of **3a-z** also showed the absence of a broad singlet of one-proton intensity at δ12.8-13.1 attributable to SH proton of the starting mercaptoaminotriazoles **2**.

Antiinflammatory activity. The compounds **3** were assessed for their antiinflammatory activity by carrageenan-induced oedema in rat paw following the technique of Winter *et al*[22]. The test compounds showed feeble to moderate activity ranging from 2.14 to 35.53%, while significant activity was observed in **3c, 3d, 3u, 3w** and **3x** taking phenylbutazone as standard which showed 58% inhibition (cf **Table I**).

Antibacterial and antifungal activities. The

Table I—Characterisation data and antiinflammatory activity of **3a-z**

Compd	R	R′	R′′	m.p. (°C)	Yield (%)	Mol. formula*	Antiinflammatory Activity (% inhibition)
3a	$CH_2C_6H_5$	OMe	H	242-43	50	$C_{20}H_{16}ClN_5OS$	4.19
3b	4-$OMeC_6H_4$	OMe	H	275-76	55	$C_{20}H_{16}ClN_5O_2S$	12.14
3c	2-MeC_6H_4	OMe	H	218-19	83	$C_{20}H_{16}ClN_5OS$	35.53
3d	Me	OMe	H	207-08	80	$C_{14}H_{12}ClN_5OS$	32.33
3e	Et	OMe	H	214-15	75	$C_{15}H_{14}ClN_5OS$	23.07
3f	*n*-Pr	OMe	H	183-84	83	$C_{16}H_{16}ClN_5OS$	12.78
3g	C_6H_5	Me	H	257-58	58	$C_{19}H_{14}ClN_5S$	8.47
3h	$CH_2C_6H_5$	Me	H	218-20	55	$C_{20}H_{16}ClN_5S$	33.82
3i	4-$OMeC_6H_4$	Me	H	258-61	50	$C_{20}H_{16}ClN_5OS$	14.28
3j	2-MeC_6H_4	Me	H	265-66	52	$C_{20}H_{16}ClN_5S$	9.09
3k	Me	Me	H	213-15	82	$C_{14}H_{12}ClN_5S$	13.98
3l	Et	Me	H	219-20	90	$C_{15}H_{14}ClN_5S$	2.14
3m	*n*-Pr	Me	H	227-28	75	$C_{16}H_{16}ClN_5S$	20.97
3n	C_6H_5	H	Me	222-23	74	$C_{19}H_{14}ClN_5S$	11.86
3o	$CH_2C_6H_5$	H	Me	180	65	$C_{20}H_{16}ClN_5S$	7.35
3p	4-$OMeC_6H_4$	H	Me	217	68	$C_{20}H_{16}ClN_5OS$	9.55
3q	2-MeC_6H_4	H	Me	259-60	77	$C_{20}H_{16}ClN_5S$	14.42
3r	Me	H	Me	275	50	$C_{14}H_{12}ClN_5S$	12.14
3s	Et	H	Me	212-13	80	$C_{15}H_{14}ClN_5S$	14.70
3t	*n*-Pr	H	Me	187	65	$C_{16}H_{16}ClN_5S$	8.12
3u	$CH_2C_6H_5$	H	H	216-17	50	$C_{19}H_{14}ClN_5S$	24.28
3v	4-$OMeC_6H_4$	H	H	222-23	56	$C_{19}H_{14}ClN_5OS$	27.81
3w	2-MeC_6H_4	H	H	256-57	51	$C_{19}H_{14}ClN_5S$	32.01
3x	Me	H	H	251-52	73	$C_{13}H_{10}ClN_5S$	28.0
3y	Et	H	H	210-11	67	$C_{14}H_{12}ClN_5S$	35.33
3z	*n*-Pr	H	H	204-05	73	$C_{15}H_{14}ClN_5S$	31.20

*All the compounds gave C, H and N analyses within ±0.4%.

antibacterial activity of the compounds **3a-z** was determined *in vitro* using paper disc method against two pathogenic micro-organisms *Escherichia coli* (Gram negative) and *Staphylococcus aureus* (Gram-positive) at 200 μg/mL and 100 μg/mL concentrations respectively, in the nutrient agar media. Out of the compounds tested **3a, d, f, g, m** and **r** exhibited a low degree of inhibition against *S. aureus* and *E. coli*.

Similarly, the antifungal screening of the compounds **3a-z** was carried out *in vitro* by paper disc method against two fungi, *Aspergillus niger* and *Candida albicans* and they did not show significant antifungal activity.

Experimental Section

General. All melting points were taken on a Buchi melting point apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Shimadzu-435 spectrophotometer using KBr disc and ^1H NMR spectra ($CDCl_3$+DMSO-d_6/TFA) on Varian T-60A and EM-390 spectrometers (60 MHz and 90 MHz) using TMS as internal standard (chemical shifts in δ, ppm). Purity of the compounds was checked by TLC on silica gel G plates and spots were visualised by iodine vapours.

2-Chloro-6-methoxy-3-(3-benzyl-5,6-dihydro-*s*-triazolo[3, 4-*b*][1, 3,4]thiadiazol-6-yl)quinoline (3a): General procedure. An equimolar mixture of 4-amino-3-benzyl-5-mercapto-*s*-triazole (1.03 g, 0.005 mole) and 2-chloro-3-formyl-6-methoxyquinoline (1.10 g, 0.005 mole) in DMF (30 mL) was stirred at 70-80°C for 12hr. On cooling, the solid-separated was filtered, washed with DMF, water and crystallized from DMF as white crystals; IR: 3370 (NH), 1628 (C=N), 1450 (C–N), 1275 (C–O–C asymmetric), 1045 (C–O–C symmetric), 815 (C–Cl), 680 (C–S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ3.9 (s, 3H, $-OCH_3$), 4.15 (s, 2H, Ar–CH_2), 5.25 (bs, 1H, NH), 6.38 (s, 1H, CH), 7.20-8.80 (m, 8H, Ar-H), 8.96 (s, 1H, ArC-4H).

Compounds **3b-z** were prepared similarly and their characterisation data are given in Table I.

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