Synthesis and Biological Activity of some Novel Quinazolonylmercaptotriazoles and their Corresponding Sulphide and Disulphide Derivatives

P. C. JOSHI, JR*., M. M. SAH and C. K. PANT

Chemical Laboratories, Kumaun University Campus, Almora-263 601

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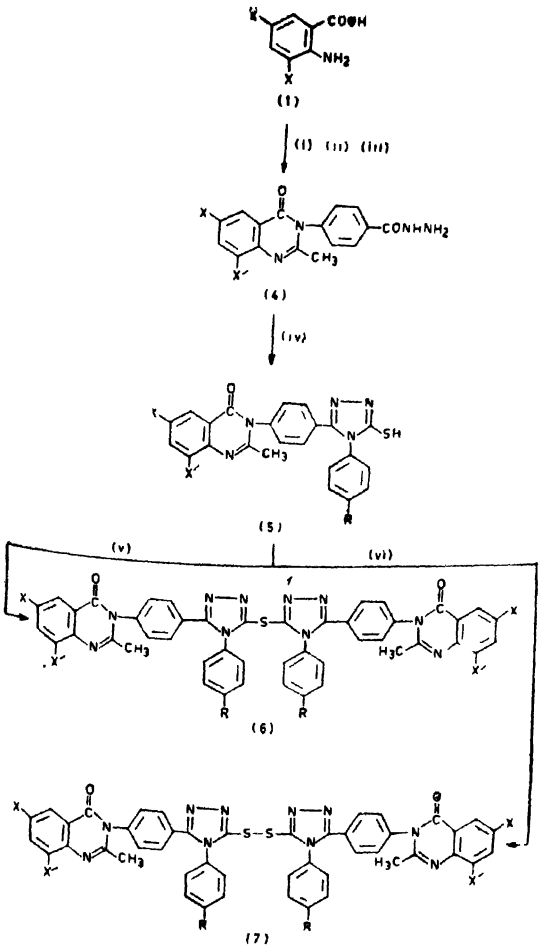
A number of 4-quinazolinones[1] and triazoles[2] have shown various biological activities. A variety of sulphides and disulphides also exhibit a broad biocidal activities[3]. The toxophoric importance of NCS moiety has been well stressed in many pesticides[4]. In view of the above facts, it was thought worthwhile to synthesise the title compounds which incorporate the above moiety. Thus compounds **4** (prepared by reported method) were treated with aryl isothiocyanates in the presence of 8% aqueous NaOH to give 4-aryl-5-[*p*-(6,8-disubstituted-2-methyl-4-oxo-3*H*-quinazolin-3-yl)phenyl]- 3-mercapto-1, 2, 4-triazoles (**5**). In addition, the triazoles (**5**) were oxidised to bis[4-aryl-5-{*p*-(6,8-disubstituted-2-methyl-4-oxo-3*H*-quinazolin - 3-yl)phenyl}-1,2,4-triazol-3-yl]



	X	X'	R
a	H	H	H
b	H	H	Cl
c	H	H	Br
d	H	H	CH_3
e	H	H	OCH_3
f	Br	H	H
g	Br	H	Cl
h	Br	H	Br
i	Br	H	CH_3
j	Br	H	OCH_3
k	Br	Br	H
l	Br	Br	Cl
m	Br	Br	Br
n	Br	Br	CH_3
o	Br	Br	OCH_3
p	I	H	H
q	I	H	Cl
r	I	H	Br
s	I	H	CH_3
t	I	H	OCH_3
u	Cl	Cl	H
v	Cl	Cl	Cl
w	Cl	Cl	Br
x	Cl	Cl	CH_3
y	Cl	Cl	OCH_3

Scheme 1. *Reagents*: (i) Ac_2O, (ii) *p*-NH_2-C_6H_4COOEt, (iii) $NH_2NH_2.H_2O$, (iv) *p*-R-C_6H_4NCS/NaOH, (v) $SOCl_2$, (vi) Br_2.

sulphide (**6**) and bis[4-aryl-5-{*p*-(6,8-disubstituted-2-methyl-4-oxo-3*H*-quinazolin-4-yl)phenyl}-1,2,4-triazol-3-yl] disulphides (**7**) by treating them with thionyl chloride and methanolic bromine, respectively (Scheme 1).

Experimental

Melting points were taken in open capillaries in a sulphuric acid bath and are uncorrected. Ir spectra (KBr) were recorded on a Perkin-Elmer spectrophotometer and pmr spectra on a EM-360 spectrometer (60 MHz) using TMS as internal standard.

Substituted-anthranilic acids[5] (**1**), 6,8-disubstituted-2-methylbenzoxazin-4-ones[6], 4-(6,8-disubstituted-2-methyl-4-oxo-3*H*-quinazolin-3-yl)ethyl benzoates[7] and 4-(6,8-disubstituted-2-methyl-4-oxo-3*H*-quinazolin-3-yl)benzhydrazides[7] (**4**) were prepared by known procedures.

Preparation of **4**: A mixture of **4a** (5.88 g, 0.02 mol) and phenyl isothiocyanate (2.70 g, 0.02 mol) was refluxed in 8% aqueous NaOH for 5–6 h. The reaction mixture was then cooled and filtered. The filtrate on acidification with cold dilute acetic acid gave a white solid which was crystallised from ethanol-water to give **5a** (5.5 g, 70%), m.p. 190° (Found : N, 16.66. $C_{23}H_{17}N_5OS$ requires : N, 17.03%) ; ν_{max} (KBr) 2 980, 2 540 (SH), 1 675, 1 600, 1 530, 815 (1,4-disubstituted benzene ring) and 770 cm^{-1} (1,2-disubstituted-benzene ring) ; δ ($CDCl_3$+DMSO-d_6) 2.1 (1H, s, SH), 2.35 (3H, s, CH_3) and 6.3–7.2 (12H, m, ArH). Other compounds were prepared similarly : **5b** (yield 69%), m.p. 258° ; **c** (71), 255° ; **d** (68), 235° ; **e** (70), 208° ; **f** (66), 196° ; **g** (68), 190° ; **h** (67), 184° ; **i** (69), 191° ; **j** (71), 196° ; **k** (66), 226° ; **l** (68), 196° ; **m** (71), 220° ; **n** (69), 196° ; **o** (66), 229° ; **p** (68), 174° ; **q** (67), 167° ; **r** (69), 192° ; **s** (71), 165° ; **t** (67), 172° ; **u** (66), 216° ; **v** (68), 170–74 ° ; **w** (70), 218° ; **x** (71), 185–90° ; **y** (69), 200°.

Preparation of **6**: Compound **5a** (2 g, 0.005 mol) was treated with thionyl chloride (10 ml) in cold and the mixture was kept at room temperature for 2 h. Thionyl chloride was then distilled off at reduced pressure and the resulting solid was washed with aqueous Na_2CO_3 and warer, dried and crystallised from ethanol to give **6a** (1 g, 50%), m.p. 225° (Found ; N, 7.96. $C_{46}H_{32}N_{10}O_2S$ requires : N, 17.76%) ; ν_{max} (KBr) 3 075, 1 670, 1 590 and 1 500 cm^{-1} ; δ (DMSO-d_6) 3.7 (6H, s, CH_3) and 6.5–8.5 (26H, m, ArH). Other compounds were prepared similarly : **6b** (yield 52%), m.p. 220° ; **c** (51), 222° ; **d** (49), 209° ; **e** (54), 245° ; **f** (53), 143–46° ; **g** (50), 170° ; **h** (51), 140° ; **i** (57), 173° ; **j** (49), 180° ; **k** (51), 160° ; **l** (48), 172° ; **m** (52), 163° ; **n** (56), 162° ; **o** (48), 170° ; **p** (47), 186° ; **q** (49), 204° ; **r** (48), 201° ; **s** (46), 193° ; **t** (49), 173° ; **u** (50), 152° ; **v** (52), 138° ; **w** (48), 154° ; **x** (47), 180° ; **y** (51), 105°.

Preparation of **7** : To an ice-cold methanolic solution of **5k** (2.85 g, 0.005 mol), a cold methanolic solution of bromine (0.8 g, 0.005 mol) was added dropwise with stirring, kept as such for 2 h and then evaporated. The resulting solid was washed successively with water, dilute NaOH and water, dried and crystallised from ethanol to yield **7k** (1.5 g, 53%), m.p. 116° (Found : N, 12.72. $C_{46}H_{28}Br_4N_{10}O_2S_2$ requires N, 12.30%) ; ν_{max} (KBr) 2 940, 1 700, 1 620 and 1 500 cm^{-1} ; δ (DMSO-d_6) 2.1 (6H, s, CH_3) and 6.0–7.7 (22H, m, ArH). Other compounds were prepared similarly : **7a** (yield 53%), m.p. 167° ; **b** (46), 156° ; **c** (47), 192° ; **d** (49), 80° ; **e** (48), 102° ; **f** (49), 213° ; **g** (51), 108° ; **h** (50), 145° ; **i** (49), 215° ; **j** (50), 160° ; **k** (53), 116° ; **l** (50), 97° ; **m** (52), 110° ; **n** (51), 98° ; **o** (49), 117° ; **p** (48), 130° ; **q** (47), 78° ; **r** (53), 82° ; **s** (54), 88° ; **t** (50), 137° ; **u** (51), 71° ; **v** (49), 106° ; **w** (46), 144° ; **x** (48), 74° ; **y** (47), 96°.

Biological screening : Compounds **5–7** were screened for their antifungal activity against *Alternaria alternata*, *Aspergillus flavus* and *Fusarium moniliforme* by paper-disc plate method[8] and none of them showed any significant antifungal activity. Compounds **5a**, **5e**, **5f**, **5i**, **5t** and **6a** were also screened *in vitro* for their antitumor activity on mouse Leukemia *p*-388 at National Cancer Institute, Bethesda, Maryland, U.S.A. and all of them were inactive at the doses tested.

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