Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2011, 3(3):288-292
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antimicrobial studies of some thiazolo [*2, 3-b*]benzo[*f*]quinazoline and thiazino[*2,3-b*]benzo[*f*]quinazoline derivatives

Ram Pal Chaudhary

Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal Distt- Sangrur, Punjab, INDIA

ABSTRACT

3, 4-dihydronaphthalen-2(1H)-one on condensation with p-tolualdehyde gives 1-benzylidene derivative which on reaction with thiourea yields 1-p-tolyl-1,2,5,6-tetrahydrobenzo[f]quinazoline-3(4H)-thione (2). The thione 2 on reaction with chloroacetic acid and 3-chloropropionic acid furnishes compounds 3, 4 and not their other possible isomers, 6 and 7 respectively. The cyclised product 3 on reaction with aromatic aldehydes produces arylidene thiazolidinones, 5 which can also be obtained directly from 2. Compounds 3 and 4 represent a novel heterocyclic system. The structural assignments of 3, 4 and 5 are based on elemental analysis, ^{1}H NMR, IR and mass spectral data. The compounds (3-5) were screened for antimicrobial activity and showed promising inhibition of S.aureus, C.diphtheriae, P.aeruginosa and E. coli bacteria.

Keywords: Thiazolidinone, antimicrobial activity, thione and arylidene derivatives.

INTRODUCTION

Quinazoline derivatives and heterocyclic annelated quinazolines are reported to be physiologically and pharmacologically active [1]. They also exhibit a wide range of activities such as anticonvulsant, anti-inflammatory, antifungal, antimalarial, and sedative [2-6]. Futher it has been reported that derivatives of quinazoline act as central nervous system depressant [7], carcinostatic [8], muscle relaxant [9, 10], antihypertensive [11], anti HIV [12 , 13], analgesic [14] and cytotoxic [15] agents. In view of the wide spectrum activities of condensed 4-thiazolidinones it was thought worthwhile to undertake the synthesis of heterocyclic systems in which 4-thiazolidinone nucleus is fused to another biologically active heterocyclic ring. The product is expected to exhibit more biological activity due to synergic effect. In continuation to our work on condensed 4-thiazolidinones [16] we wish to report here the reaction of 1-p-tolyl-1,2,5,6-tetrahydrobenzo[f]quinazoline-3(4H)-thione (2) with haloacids furnishing benzo[f]thiazolo[2,3-b] quinazoline system and benzo[f]thiazino[2,3-b] quinazoline system (cf. Scheme 1) and biological evaluation of the cyclized compounds.

MATERIALS AND METHODS

All the chemicals used were purchased from Sigma Aldrich and were used as such without further purification. Melting points were determined in sulphuric acid bath and are uncorrected. TLC was performed on silica gel G plates using benzene-ethyl acetate (4:1) as irrigant and iodine vapours as visualizing agent. IR spectra were recorded in nujol mull on a Perkin–Elmer RXI FTIR spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR in $CDCl_3$ on Bruker Advance II 400 MHz spectrometer using TMS as internal reference (chemical shift in δ, ppm) and mass spectra on Q-TOF MS/ES spectrometer. The elemental analysis (C, H, N) of compounds was performed on a Carlo Erba-1108 elemental analyzer.

Experimental

1-(4-Methylbenzylidene)-3, 4-dihydronaphthalen-2(1H)-one (1)

A mixture of 2-tetralone (7.3 g, 0.05 mol) and p-tolualdehyde (6.0 g, 0.05 mol) in gl. acetic acid (25 ml) and conc. HCl (15 ml) was kept at 0^0 C for 72 hr. The solid obtained was filtered and washed well with pet. ether. Crystallization from ethanol furnished 1 as shining cream colored needles. m.p. 85-90^0C, yield 7.2 g (61%); IR (KBr):1680 (C=O); ^1H NMR ($CDCl_3$): δ 2.41(3H,s, CH_3), 2.93 (2H, t, CH_2 J=6.16 Hz), 3.10 (2H, t, CH_2, J=6.68 Hz), 6.92-7.46 (8H, m, Ar-H), 7.81 (1H, s, H_A). Anal. Calcd (%) for $C_{18}H_{16}O$ (248): C, 87.09; H, 6.45. Found (%): C, 87.05; H, 6.42.

1-p-Tolyl-1, 2, 5, 6- tetrahydrobenzo[f]quinazoline-3(4H)-thione (2)

A mixture of 1-(4-methylbenzylidene)-3,4-dihydronaphthalen-2(1H)-one 1 (4.96 g, 0.02 mol), and thiourea (1.52 g, 0.02 mol) in ethanolic potash (2.0 g KOH in 75 ml ethanol) was heated under reflux for 5 hr. The volume of the reaction mixture was reduced to half and kept overnight and the concentrate poured into ice-cold water. The solid, thus obtained, was filtered, washed well with water and finally crystallized from DMF-ethanol to give 2. m.p. 125-30^0C, yield 4.0 g (68%); IR (KBr): 1210 (C=S), 3220 (NH), 1654 (C=C); ^1H NMR ($CDCl_3$): δ 2.43 (3H, s, CH_3), 2.04-2.19 (2H, m, CH_2), 2.67-2.83 (2H, m, CH_2), 5.88 (1H, s, H_A), 6.85-7.95 (8H, m, Ar-H). Anal. Calcd (%) for $C_{19}H_{18}N_2S$ (306): C, 74.50; H, 5.88; N, 9.15; S, 10.45. Found (%): C, 74.48; H, 5.85; N, 9.16; S, 10.42.

12-p-Tolyl-9, 12-dihydro-5H- benzo [f] thiazolo[2,3-*b*] quinazoline-10(6H)-one (3)

A mixture of thione 2 (3.06 g, 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol), anhyd. sodium acetate (0.82 g, 0.01mol), gl. acetic acid (10 ml) and acetic anhydride (2 ml) was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and then poured into water to afford a solid. The solid, thus obtained, was filtered, washed well with water and purified by passing through a silica gel column using pet. ether as eluant, m.p. 175^0-178^0C, yield 1.8 g (55%); IR(KBr): 1579, 1619 (C=C, C=N), 1726 (N-C=O); ^1H NMR ($CDCl_3$): δ 2.44 (3H, s, CH_3), 2.03-2.20 (2H, m, CH_2), 2.67-2.79 (2H, m, CH_2), 3.67-3.83 (2H,d d, SCH_2, J=17.2 Hz), 6.52 (1H, s, H_A), 6.82-7.98 (8H, m, C_6H_5). MS: 347 $[M+1]^+$ (100%), $[M+2]^+$ (64.9%). Anal. Calcd (%) for $C_{21}H_{18}N_2OS$ (346): C, 72.83; H, 5.20; N, 8.09; S, 9.24. Found (%): C, 72.80; H, 5.23; N, 8.04; S, 9.21.

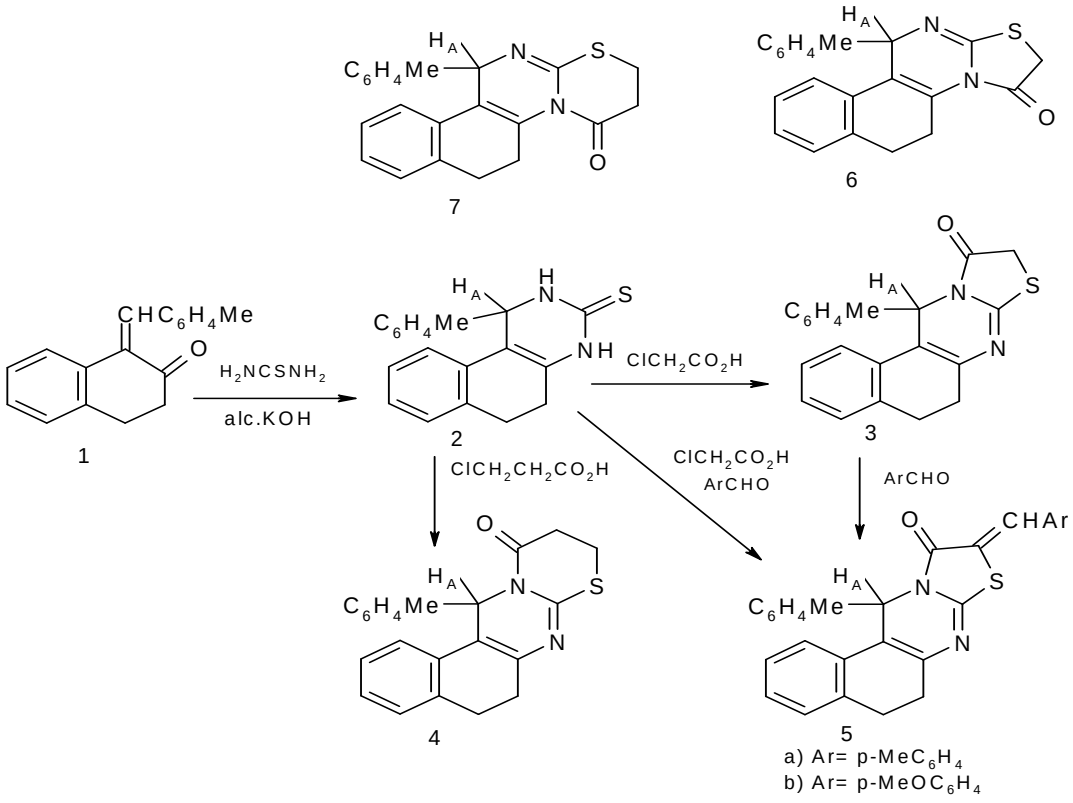
13-p-Tolyl-5, 6, 9, 10-tetrahydrobenzo[f] [1,3] thiazino[2,3-*b*] quinazolin-11(13H)-one (4)

A mixture of thione 2 (3.06 g, 0.01 mol), 3-chloropropionic acid (1.08 g, 0.01 mol), anhyd. sodium acetate (0.82 g, 0.01 mol), gl. acetic acid (15 ml) and acetic anhydride (3 ml) was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid, thus obtained, was filtered, washed with water and crystallized from ethanol furnishing 4 as shinning needles, mp 190-94^0C, yield 1.70g (50%); IR (KBr): 1620

(C=C, C=N) and 1685 (N-C=O). ^{1}H NMR ($CDCl_3$): δ_H 2.42 (3H, s, CH_3), 2.82 (2H, t, CH_2, *J*= 7.18 Hz), 2.96 (2H, t, CH_2, *J*= 7.16 Hz), 3.08 (2H, t, $COCH_2$, *J*= 7.50 Hz), 3.15 (2H, t, SCH_2, J=7.48), 6.54 (1H, s, H_A), 6.84-7.92 (8H, m, Ar-H); MS 361 $[M+1]^+$; 54.4%). Anal. Calcd for $C_{22}H_{20}N_2OS$ (%) (360): C, 73.33; H, 5.55; N 7.77; S, 8.88, Found (%): C, 73.30; H, 5.56; N, 7.74; S, 8.84%.

(z)-9-(4-Methylbenzylidene)12-p-tolyl-9,12-dihydro-5H-benzo[f]thiazolo[2,3-*b*]quinazolin-10[6H]-one 5(a)

i) A mixture of thiazolidinone 3 (0.692 g, 0.002 mol), p-tolualdehyde (0.24 g, 0.002 mol), anhyd. sodium acetate (0.16 g, 0.002 mol) and gl. acetic acid (10 ml) was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The solid thus obtained, was filtered and washed well with water and finally crystallized from gl. acetic acid to give 5a. m.p. 208-10^{0}C, yield 0.5 g (57%); IR(KBr): 1704 (C=O), 1582, 1653 (C=C, C=N); ^{1}H NMR ($CDCl_3$): δ 2.42 (3H, s, CH_3), 2.13-2.26 (2H, m, CH_2), 2.64-2.72 (2H, m, CH_2), 2.48 (3H, s, CH_3), 6.67 (1H, s, H_A), 7.05-7.95 (13H, m, C_6H_5), 8.20 (IH, s, H_B). Anal. Calcd (%) for $C_{29}H_{24}N_2OS$ (448): C, 77.67; H, 5.35; N, 6.25; S, 7.14. Found (%): C, 77.63; H, 5.32; N, 6.23; S, 7.10.



Scheme 1

Compound 5b was similarly prepared from compound 3 and p-anisaldehyde.

5b. m.p. 194-98^{0}C, yield 52%; IR(KBr): 1700 (C=O), 1552, 1576 (C=C, C=N); ^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s, CH_3), 2.20-2.28 (2H, m, CH_2), 2.58-2.68 (2H, m, CH_2), 3.94 (3H, s, OCH_3), 6.63 (1H, s, H_A), 7.16-7.88 (13H, m, C_6H_5), 8.24 (1H, s, H_B). Anal. Calcd (%) for $C_{29}H_{24}N_2O_2S$ (464): C, 75.00; H, 5.17; N, 6.03; S, 6.89. Found (%): C, 74.96; H, 5.20; N, 6.01; S, 6.86.

ii) A mixture of thione 2 (0.306 g, 0.001 mol), chloroacetic acid (0.09 g, 0.001 mol) and p-tolualdehyde (0.14 g, 0.001 mol) and anhyd. sodium acetate (0.16 g, 0.002 mol) in gl. acetic acid (10 ml) and acetic anhydride (2 ml) was refluxed for 2 hr. A similar work up as in (i) gave 5a, mp 206-08^{0}C which remained undepressed when mixed with the compound obtained by method (i) , yield 52%, 0.32g.

Compound 5b was similarly prepared from compound 2 and p-anisaldehyde following the above procedure and the product obtained was found to be the same as obtained by following the procedure (i).

RESULTS AND DISCUSSION

1-(4-methylbenzylidene)-3, 4-dihydronaphthalen-2(1H)-one (1) , obtained by the reaction of 3, 4-dihydronaphthalen-2(1H)-one and p-tolualdehyde, when condensed with thiourea gave (2). The unsymmetrical thione (2) on reaction with chloroacetic acid followed by cyclization of the intermediate *in situ* was likely to give 3 or (6) or both depending on the mode of cyclization. However, the thione (2) when reacted with chloroacetic acid gave a single product (TLC). The appearance of a band at 1726 cm^{-1} (N-C=O) in the IR spectrum and exhibition of [M+1] at m/z 347 (100%) in the mass spectrum of the TLC- pure product suggested that the cyclization had indeed taken place. The IR and mass spectral data were of little help in deciding in favour of either structure 3 or 6. However, the structure 3 was finally assigned to this cyclization product in preference to the structure 6 on the basis of ^{1}H NMR spectral data. If the structure 6 is correct for the cyclization product, obtained from 2 and chloroacetic acid, then H_A will resonate in the same region as that of thione 2. On the other hand if the structure 3 is correct, H_A will be deshielded by the carbonyl group of the thiazolidinone ring and H_A will resonate downfield in comparison to H_A of thione 2. The H_A of thione 2 resonates at δ 5.88 whereas the singlet at 6.52 assignable to H_A in the ^{1}H NMR spectrum of the cyclization product strongly supports the structure 3 and rules out the other alternate structure 6 from which such a downfield shift is not expected.

3-chloropropionic acid in place of chloroacetic acid in the above reaction, afforded another heterocyclic system. The reaction of thione 2 with 3-chloropropionic acid although capable of giving both the isomers, yielded only one product (TLC) which can be represented either by 4 or 7. The absorbtion at 1685 cm^{-1} (N-C=O) and the exhibition of a molecular ion peak [M+1] at m/z 361 (83.6%) in the IR and mass spectra respectively of the TLC pure product confirm that the cyclization had indeed occurred. The singlet at δ 6.54 assignable to H_A in the ^{1}H NMR spectrum of the TLC pure product being downfield in comparison to δ 5.88 (due to H_A) in the thione 2 supports the structure 4 for the cyclization product in preference to structure 7 from which such a downfield shift is not expected.

Arylidene thiazolidinones (5) were prepared by two routes. In the first approach, the thiazolidinone 3 was condensed with aldehydes to give arylidene thiazolidinones (5a-b) while in the second approach 5a was obtained directly by heating 2 with chloroacetic acid and *p*-tolualdehyde. The structures 5a-b were established by IR and ^{1}H NMR spectral data. The parent thiazolidinone (3) exhibited an absorption band at 1726 cm^{-1} (N-C=O), but the unsaturation at the 2-position being conjugated with the carbonyl group at the 3-position as in arylidene thiazolidinones (5a-b) produced a bathochromic shift [17] as expected. The absence of a signal due to methylene protons (SCH_2) and the display of singlets at δ 8.20 and 8.24 assignable to the benzal proton H_B in the ^{1}H NMR spectra of compounds, obtained from the condensation of 3

with p-tolualdehyde and p-anisaldehyde respectively were tenable with the proposed structures 5a, b.

Antimicrobial studies

The compounds (3-5) were screened for their antimicrobial activity against gram-negative bacteria, *E. Coli* and *P. aeruginosa* and gram-positive bacteria, *S. aureus*, and *C. diphtheriae* using disc diffusion method [18, 19] (Table 1). The zone of inhibition was measured in mm and the activity was compared with standard drug.

Table1. Antibacterial activity studies by drug diffusion method

S. No.	Compound	Zone of inhibition (in mm)			
		Gram Positive		Gram Negative	
		S.aureus	*C.diphtheriae*	*P.aeruginosa*	*E.coli*
1.	3	15	16	15	12
2.	4	13	14	13	10
3.	5a	12	13	13	12
4.	5b	14	14	17	16
5.	Ampicillin trihydrate	26	28	24	21
	DMSO	00	00	00	00

CONCLUSION

The regiochemistry of the cyclised products was established by spectroscopic methods and the orientation of the cyclization in 3 and 4 was confirmed by ^{1}H NMR spectroscopy. All the compounds have shown promising activity but compound 3 has been found to possess maximum activity.

REFERENCES

[1] V. J. Ram, B. K. Tripathi, A. K. Srivastava, *Bioorg. Med. Chem*. **2003**, 11, 2439.
[2] A. Dandia, R. Singh, P. Sarawgi, *J. Chin. Chem. Soc.*, **2007**, 54, 445.
[3] S. M. Mosaad, K. I. Mohammed, S. G. Abdel-Hamide, *J. Biol. Sci*. **2004**, 4, 504.
[4] P. M. S. Bedi, V. Kumar, M. P. M. Ahajan, *Bioorg. Med.Chem. Lett.* **2004**, 14, 5211.
[5] Y. Jin, H. Li, L. Lin, J. Tan, J. Ding, X. Luo, Y. Lang, *Bioorg. Med. Chem.* **2005**, 13, 5613.
[6] A.K. Bhaltacharjee, M.G. Hartell, D.A. Nichals, R.P. Hicks, B.Stanton, F.E. Vanhamont, V.K. Milhous, *Eur. J. Med. Chem*. **2004**, 39, 59.
[7] P.H.L. Wei and S.C. Bill, U.S. Patent 3 475 424, 1970; *Chem. Abstr*., **1970**, 72, 31850.
[8] R.C. Elderfield and R.N. Prasad, *J. Org. Chem.*, **1959**, 24, 1410.
[9] Y. Kuwada, T. Sonda and K. Mugnno; *Chem. Abstr*., **1976**, 84, 44177.
[10] J.B. Hunter, U.S. Patent 3 897 446, 1976; *Chem. Abstr*., **1976**, 84, 44183.
[11] K.C. Lier and L.Y. Hsu, *Arch. Pharm*. Wemheim Gen, **1985**, 502.
[12] J. Balzarini, B. Orzeszko, J.K. Maurin, A. Orzeszko, *Eur. J. Med. Chem*., **2007**, 42, 993.
[13] A. Rao, A. Chimirri, A.M. Monforte and M. Zappala, *ARKIVOC*, **2004**, (v), 147.
[14] L.J.S. Knutsen, C.J. Hobbs, C.G. Earnshaw, *Bioorg. Med. Chem. Lett*., **2007**, 17, 662.
[15] V.P.M. Rahman, S. Mukhtar and W.H. Ansari, *Eur. J. Med. Chem*., **2005**, 40, 173.
[16] H. Kumar, and R. P. Chaudhary, *J. Chem. Pharm. Res.* **2010**, 2(3), 667-72.
[17] H.M. Randall, N. Fuson, J.R. Dangle; Infrared determination of organic structures, (Van Nostrand, New York, **1949)**.
[18] R. Cruickshank, J.P. Duguid, B.P. Marmion, 12th (Ed), *Medicinal Microbiology*, (Churchill Livingstone: London, **1975)** 11.
[19] B.A. Arthington, M. Motley, C.J. Morrison, *J. Clin. Microbiology*, **2000**, 38, 2254.