DEVELOPMENT OF NEW MOLECULAR ENTITIES AS POTENT NON-STEROIDAL NON-ACIDIC ANTI-INFLAMMATORY AGENTS – PART-I: SYNTHESIS OF SOME SUBSTITUTED PYRAZOLO-[3, 4-a] THIOZOLO [2', 3'-b] QUINAZOLINES

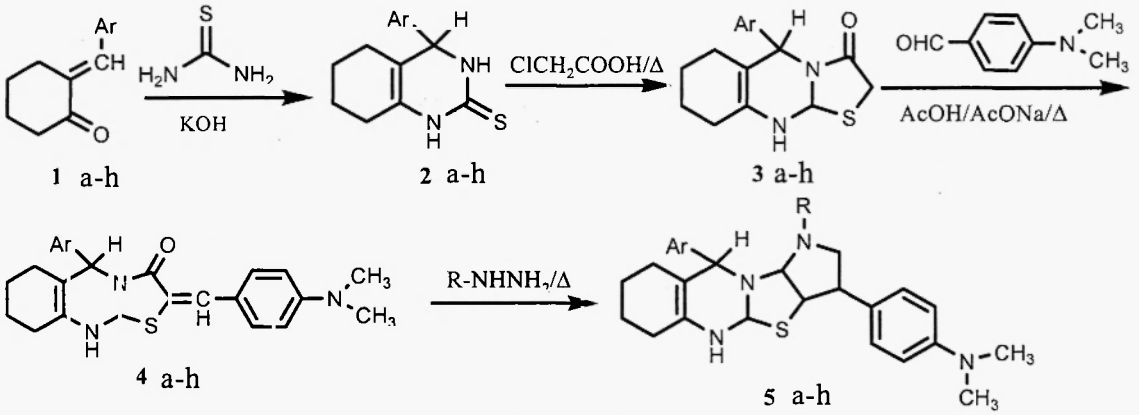
Kalyan Chakravarthy Akula[$] Suresh Tatikonda and Malla Reddy Vanga*
Medicinal Chemistry Research Laboratory, University College of Pharmaceutical Sciences,
Kakatiya University, Warangal-506009, India.
[$] kalyanca@drreddys.com
[$]Present Address: Dr.Reddy's Laboratories limited, III floor, D # 7-1-27 Ameerpet, Hyderabad – 016, India.

Abstract : Eight 6-aryl-2,3,4,5-tetrahydro-7,8,9,10-tetrahydro-11H-pyrazolo [3,4-a] thiazolo [2,3-b] quinazolines were prepared **5a-h** from the respective 5H-5-aryl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazolin-3(2H)-ones by a cycloaddition reaction of hydrazine / phenylhydrazine. The thiazoloquinazolinones, on the other hand were obtained from a fusion reaction of 4-aryl-3,4,5,6,7,8-hexahydroquinazonin-2-thiones with chloroacetic acid. The final compounds were purified and characterized by their analytical and spectral (IR & ^{1}HMR) data. Their pharmacological studies are in progress.

Introduction

Nitrogen-bridged heterocycles are known to be important medicinal agents. A fused heterocyclic 'apazone' is distinctly related to an anti-inflammatory agent 'cintrazone' which could be viewed as a cyclized derivative of phenylbutazone, the activity of the proto-type being retained.[1] In recent years, the synthesis and anti-inflammatory activity of indenothiazoles and indole-thiazolidinones were reported.[2,3] The quinazolines and pyrazolines are well known for their broad spectrum of biological activities.[4,5] Therefore, it has been thought worth-while to develop new molecular entities containing all these important pharmacophores, viz., quinazoline, pyrazoline and thiazoline along with (*p*-N,N-dimethylamino)phenyl groups. It has been designed to achieve the synthesis of such molecular entities by simple synthetic manouvers with a view to study them for their anti-inflammatory potency. We present in this communication the work pertaining to the synthesis of the title compounds. Meanwhile, a detailed pharmacological evaluation of the toxicity and anti-inflammatory activity are undertaken and the results will be published elsewhere. Synthesis of the newly designed molecules has been achieved as given in Scheme–I.

For this purpose, different 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thiones (**2**) were prepared by the condensation of appropriate 2-arylidenecyclohexanones (**1**) with thiourea in the presence of base. They were purified and characterized by their analytical and spectral data. IR spectra (KBr) exhibited characteristic absorption bands at (cm^{-1}): 1210 (C=S), 1555 (C-N) and 3175 (2x NH, cyclic); ^{1}H-NMR spectrum ($CDCl_3$), showed signals at (δ, ppm): 1.80 – 2.30 (m, 8H, 4 x CH_2, cyclohexane), 5.14 (s, 1H, CH), 5.85 (s, 2H, two cyclic – NH, D_2O exchangeable) and 7.2 – 7.8 (m, 5H Ar-H).



Scheme-1

Substitution	R	Ar
a	H	C_6H_5
b	H	*p*-OHC_6H_4
c	H	*p*-ClC_6H_4
d	H	*p*-$OMeC_6H_4$
e	C_6H_5	C_6H_5
f	C_6H_5	*p*-OHC_6H_4
g	C_6H_5	*p*-ClC_6H_4
h	C_6H_5	*p*-$OMeC_6H_4$

Each of the quinazolin-2-thiones (**2 a-d**) were then subjected to a fusion reaction with chloroacetic acid. The product obtained in each case was characterized as the respective 6,7,8,9-tetrahydro-5H-5-aryl-thiazolo [2,3-b] quinazolin-3(2H)-one, on the basis of its analytical and spectral data. IR spectra (KBr) of the compounds exhibited characteristic bands at (cm^{-1}): 1710 (-N-C=O, cyclic), 1605 (C=C). They also showed conspeciuous absence of an absorption band at ~3175 characteristic of –NH indicating their involvement in thione-thiol tautomerism and then in cyclization reaction. ^{1}H-NMR spectra (DMSO-d_6), showed characteristic peaks at (δ, ppm): 1.60 – 2.58 (m, 8H, 4 x CH_2, cyclic), 4.82 (s, 2H, -S-CH_2-CO-), 5.63 (s, 1H, C_5-H) and 6.98 – 7.82 (m, 5H Ar-H).

Each of the thiazolo-quinazolinones (**3**) was subjected to a condensation reaction with p-(N,N-dimethylamino)benzaldehyde by heating in acetic acid over anhydrous sodium acetate, and the product obtained was characterized as the corresponding 2-p(N,N-dimethylamino)benzylidene derivative (**4a**), on the basis of analytical and spectral data. IR spectra (KBr) of the product exhibited characteristic absorption bands at (cm^{-1}) : 1705 (N-C=O, cyclic), 600 (C=C) and 1595 (C=N), ^{1}H-NMR spectra ($CDCl_3$) of these compounds showed proton absorption signals at (δ, ppm) : 6.52 (s, 2H, -S-CH_2-), 5.76 (s, 1H, C_5-H), 1.63 – 2.04 (m, 8H, 4 x –CH_2, cyclic), 2.84 (s, 6H, NMe_2), 8.37 (s, 1H, benzylidene –CH) and ~7.06 – 7.3 (m, 5H Ar-H). Mass: m/e: 417.19 (M+1, 100.0%).

Condensation reaction of hydrazine / phenylhydrazine with 2-p-(N,N-dimethyl amino)benzylidene]5H-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2H)-ones (4) : Each of the compounds (**4**) was then subjected to a condensation reaction with hydrazine hydrate / phenylhydrazine by heating under reflux over anhydrous sodium acetate for 6 h. The single product obtained in such a reaction was purified by recrystallization from alcohol and characterized as the respective cycloaddition-elimination product, 6-phenyl-10-[p-(N,N-dimethylamino)phenyl]-2,3,4,5-tetrahydro-7,11-dihydro-9,10-dihydro-pyrazolo[3,4-d]thiazolo[2,3-b]quinazolin (**5a**), ^{1}HMR spectra ($CDCl_3$) of the compound showed proton absorption signals at (δ, ppm) : 1.63 – 2.04 (m, 8H, 4 x $-CH_2$, cyclic), 1.77 (t, 1H, CH), 2.86 (m, 1H, CH), 2.85 (s, 6H, NMe_2), 3.04 (d, 2H, CH_2), 3.14 (d, 1H, CH) 4.59 (s,1H,-CHPh) and 7.06 – 7.3 (m, 5H, Ar-H). Mass: m/e: 432.23 (M+1, 100.0%).

Its IR spectrum exhibited the absence of oxo group and exocyclic double bond, the additional peak at 3180 cm^{-1} corresponds to the additional –NH, indicating their involvement in cycloaddition-elimination reaction.

Experimental

Melting points were determined in open capillaries and are uncorrected. Purity of compounds was checked by TLC and IR spectra were recorded on Perkin-Elmer model-1600 spectrophotometer. ^{1}H NMR spectra of the compounds were recorded on Perkin-Elmer EM-390-200 MHz spectrophotometer, using TMS as an internal standard.

The required 2-arylidene-cyclohexanones (**1**) viz., benzylidene, 4-chlorobenzylidene, 4-hydroxybenzylidene and 4-methoxybenzylidene were prepared from cyclohexanone and appropriate aldehyde by a standard procedure.[6]

Synthesis of 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thiones (2) – General Procedure: A mixture of 2-arylidene cyclohexanone (0.01 mole), thiourea (0.01 mole) and an alcoholic solution of potassium hydroxide (6g in 150 mL alcohol), were taken into a reaction flask and heated under reflux for 3h. The volume of the mixture was reduced to half by distilling-off excess alcohol. The concentrate was diluted with cold water and cooled further. The resultant clear solution was then acidified carefully with dilute acetic acid and kept in ice-chest, overnight. The solid thus resulted was filtered washed with small portions of cold water and dried; it was purified by recrystallization from alcohol.

Synthesis of 5H-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2H)-ones (3) – General Procedure: Chloroacetic acid (0.01 mole) was taken in a clean dry reaction flask, melted on water bath and a fine powder of appropriate thione (**2**) (0.01 mole) was added to it, in small portions at a time while shaking to achieve homogeneity. The reaction mixture was then heated on a water-bath for an hour and then cooled and kept in ice-chest, over night. It was triturated with cold water and the product was filtered, washed thoroughly with ice-cold water and dried. The resultant compound was purified by recrystallization from alcohol.

Synthesis of 2-[p(N,N-dimethylamino)-benzylidene]-5H-5-aryl-6,7,8,9-tetrahydro thiazolo[2,3-b] quinazolin-3(2H)-ones (4) – General Procedure : A mixture of thiazolo-quinazoline-3(2H)-one (**3**) (0.01 mole), p-(N,N-dimethylamino)benzaldehyde (0.01 mole) and freshly fused sodium acetate (0.01 mole) in glacial acetic acid (20 ml) was heated under reflux for 2h. The reaction mixture was left overnight and the solid thus separated was filtered, washed with cold water and dried. The resulted compound was purified by recrystallization from alcohol. (**Table-3**)

Adopting this procedure four different 2-[p-(N,N-dimethyl amino)benzylidene) tetrahydro-thiazolo-quinazolines (**4**) were prepared.

Synthesis of 6-Aryl-10-[p(N,N-dimethyl-amino)phenyl]-2,3,4,5-tetrahydro-7, 8, 9, 10-tetrahydro-11H-pyprazolo[3,4-d]thiazolo[2,3-b]quinazolines and their 8-phenyl analogs (5) – General Procedure : An equimolar mixture (0.001 mole each) of benzylidene-quinazolinone (**IV**) and hydrazine hydrate/phenylhydrazine was taken into a clean and dry reaction vessel and freshly fused sodium acetate (1.0g) was added. The reaction mixture was heated under reflux for 4h. It was cooled and triturated with ice-cold water. The resultant product was filtered, washed repeatedly with ice cold water and dried. It was purified by recrystallization from alcohol.

The physical and analytical data of compounds of **2, 3, 4** and **5** are presented in Tables 1, 2, 3 and 4 respectively.

Table–1 : Physical and analytical data of 4-aryl-3-4, 5, 6, 7, 8-hexahydro-quinazolin-2-thiones (**2 a-d**).

Compd. No.	M.R. °C	Mol. Formula	Yield (%)	Elemental Analyses Observed (Calc.)		
				C	H	N
2a	243-245	$C_{14}H_{16}N_2S$	72	68.89 (68.81)	6.51 (6.60)	11.41 (11.46)
2b	247-249	$C_{14}H_{16}N_2OS$	53	64.45 (64.58)	6.07 (6.19)	10.85 (10.76)
2c	251	$C_{14}H_{15}N_2SCl$	62	60.44 (60.31)	5.54 (5.42)	9.89 (10.05)
2d	250	$C_{15}H_{18}N_2OS$	57	65.71 (65.66)	6.52 (6.61)	10.30 (10.21)

Table–2 : Physical and analytical data of 6, 7, 8, 9-tetrahydro-5H, 5-aryl-thazolo [2,3-b]-quinazolin-3(2H)-ones (**3 a-d**)

Compound No.	M.p. °C	Mol. Formula	Yield (%)	Elemental Analyses Observed (Calc.)		
				C	H	N
3a	112	$C_{16}H_{16}N_2OS$	69	67.69 (67.58)	5.61 (5.67)	9.74 (9.85)
3b	146	$C_{16}H_{16}N_2O_2S$	58	63.85 (63.98)	5.40 (5.37)	9.29 (9.33)
3c	128	$C_{16}H_{15}N_2OSCl$	65	60.34 (60.28)	4.88 (4.74)	8.91 (8.79)
3d	119	$C_{17}H_{18}N_2OS$	63	68.51 (68.42)	6.21 (6.08)	9.31 (9.39)

Table–3 : Physical and analytical data of 2-(*p*(-N,N-dimethylamino benzylidene)-5H-5-aryl-6,7,8,9 tetrahydro thiazolo[2,3-b]quinazolin 3(2H)-ones (**4 a-d**)

Compound No.	M.p. °C	Mol. Formula	Yield (%)	Elemental Analyses Observed (Calc.)		
				C	H	N
4a	87	$C_{25}H_{25}N_3OS$	73	72.74 (72.26)	6.01 (6.06)	10.14 (10.11)
4b	108	$C_{25}H_{25}N_3O_2S$	68	69.61 (69.58)	5.91 (5.84)	9.51 (9.65)
4c	92	$C_{25}H_{24}ON_3SCl$	59	66.67 (66.73)	5.41 (5.38)	9.28 (9.34)
4d	98	$C_{26}H_{27}N_3O_2S$	60	69.95 (70.08)	6.01 (6.11)	9.47 (9.43)

Table–4 : Physical and analytical data of 6-aryl-(*p*-N,N-dimethylamino phenyl)-2,3,4,5-tetrahydro 7,8,9,10- tetrahydro -11H-pyrazolo-[2,3-b]quinazolines and their 8-phenyl analogs (**5 a-g**)

Comp. No.	R	M.P. °C	Mol. Formula	Yield (%)	Elemental Analyses Observed (Calc.)		
					C	H	N
5a	H	125	$C_{31}H_{33}N_5S$	67	73.36 (73.34)	6.49 (6.55)	13.78 (13.79)
5b	H	153	$C_{31}H_{33}N_5OS$	58	71.22 (71.10)	6.31 (6.35)	13.46 (13.37)
5c	H	142	$C_{31}H_{24}N_2SCl$	53	75.51 (75.67)	4.83 (4.92)	5.69 (5.76)
5d	H	134	$C_{32}H_{35}N_2OS$	63	77.64 (77.54)	6.49 (5.65)	5.68 (5.65)
5e	Ph	116	$C_{25}H_{28}N_5OS$	57	69.35 (67.24)	6.69 (6.32)	16.36 (15.62)
5f	Ph	138	$C_{25}H_{25}N_5OS$	56	67.78 (67.69)	6.71 (5.68)	15.68 (15.79)
5g	Ph	130	$C_{25}H_{27}N_5SCl$	59	64.25 (64.57)	5.81 (5.85)	14.91 (15.07)
5h	Ph	123	$C_{26}H_{27}N_3O_2S$	61	70.14 (70.08)	6.09 (6.11)	9.41 (9.43)

Acknowledgements

The authors are thankful to the authorities of Kakatiya University, Warangal for the facilities and encouragement.

References

1. A. Stoll and Hofmann, in 'Chemistry of Alkaloids', Ed. S.W. Pelletier, Van Nostrand Reinold & Co. New York, p.267 (1970).
2. R. Gupta, S. Sudan, G.B. Singh, S. Bani and P.L. Kachroo, *Indian J. Pharm. Sci.* **53**, 245 (1991).
3. A.C. Bajji, K.P. Channa Basavaraj and K.M.K. Swamy, *Indian Drugs* **31**, 270 (1994).
4. A. Malla Reddy, Y. Jayamma, P. Ravinder Reddy and V.M. Reddy, *Indian Drugs* **25**, 187, (1988).
5. T.C. Sharma, M.M. Bakadia and M J. Reddy, *Indian J. Chem.* **19B**, 228, (1980).
6. A. Malla Reddy, R. Raja Reddy and V.M. Reddy, *Indian J. Pharm. Sci.* **53**, 229, (1991).
7. G. Achaiah, R. Raja Reddy, Y. Jayamma and V.M. Reddy, *Indian J. Pharm. Sci.* **53** (1991), 197.

Received on Marcy 11, 2006