[e006]

Efficient Niementowski synthesis of novel derivatives of 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]-quinazolin-7-one

Sachin S. Laddha* and Satayendra P. Bhatnagar

Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, India, e-mail: pinkumanno@rediffmail.com.

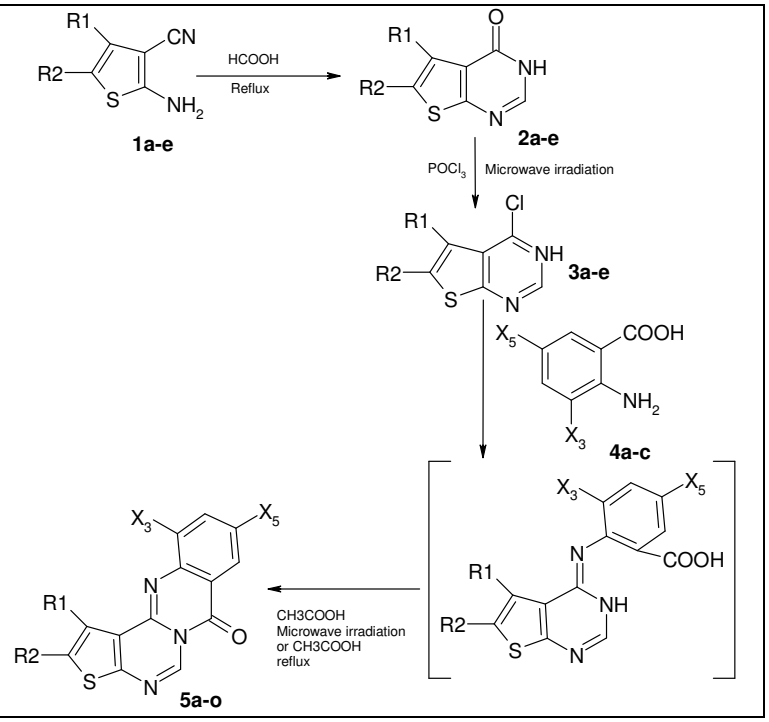
Abstract

Starting Starting from 5,6-disubstituted-3*H*-thieno[2,3-d]pyrimidin-4-ones, novel 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-ones could be reached in two steps through a von Niementowski reaction, which involves condensation of substituted anthranilic acids with a 4-chloro-5,6-disubstituted-3*H*-thieno[2,3-*d*] pyrimidines. Microwave irradiation in acetic acid media was used in order to improve reactions where conventional heating was limited.

Graphical Abstract

Efficient Niementowski synthesis of novel derivatives of 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]-quinazolin-7-one

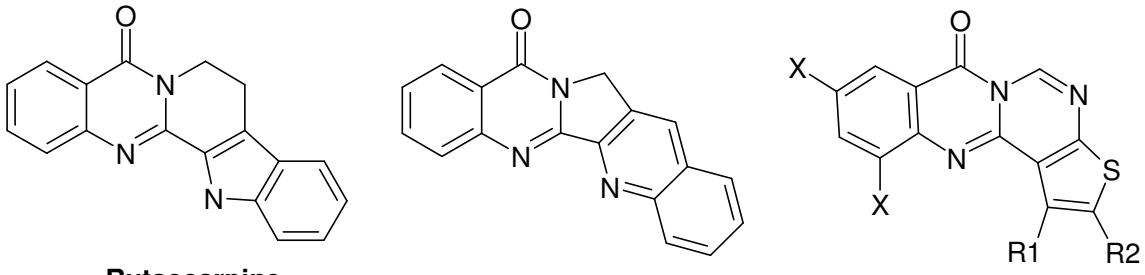
Sachin S. Laddha and Satayendra P. Bhatnagar*



Keywords: cyclization; fused thieno-[2,3-d]-pyrimidine; Microwave assisted synthesis; Sulphur heterocycles.

Introduction

Literature survey has revealed the diversified biological and pharmacological significance of several nitrogen and sulphur heterocycles. This aspect has been drawing the attention of many researchers towards exploiting the biological importance of various heterocyclic compounds and to establish the relationship between their biological, pharmacological potency and structural features. A rapid progress in the work on fused quinazolinones and thienopyrimidines has given rise to a number of compounds exhibiting potent pharmacological actions.



Rutaecarpine **Luotonine** **5**

Figure 1

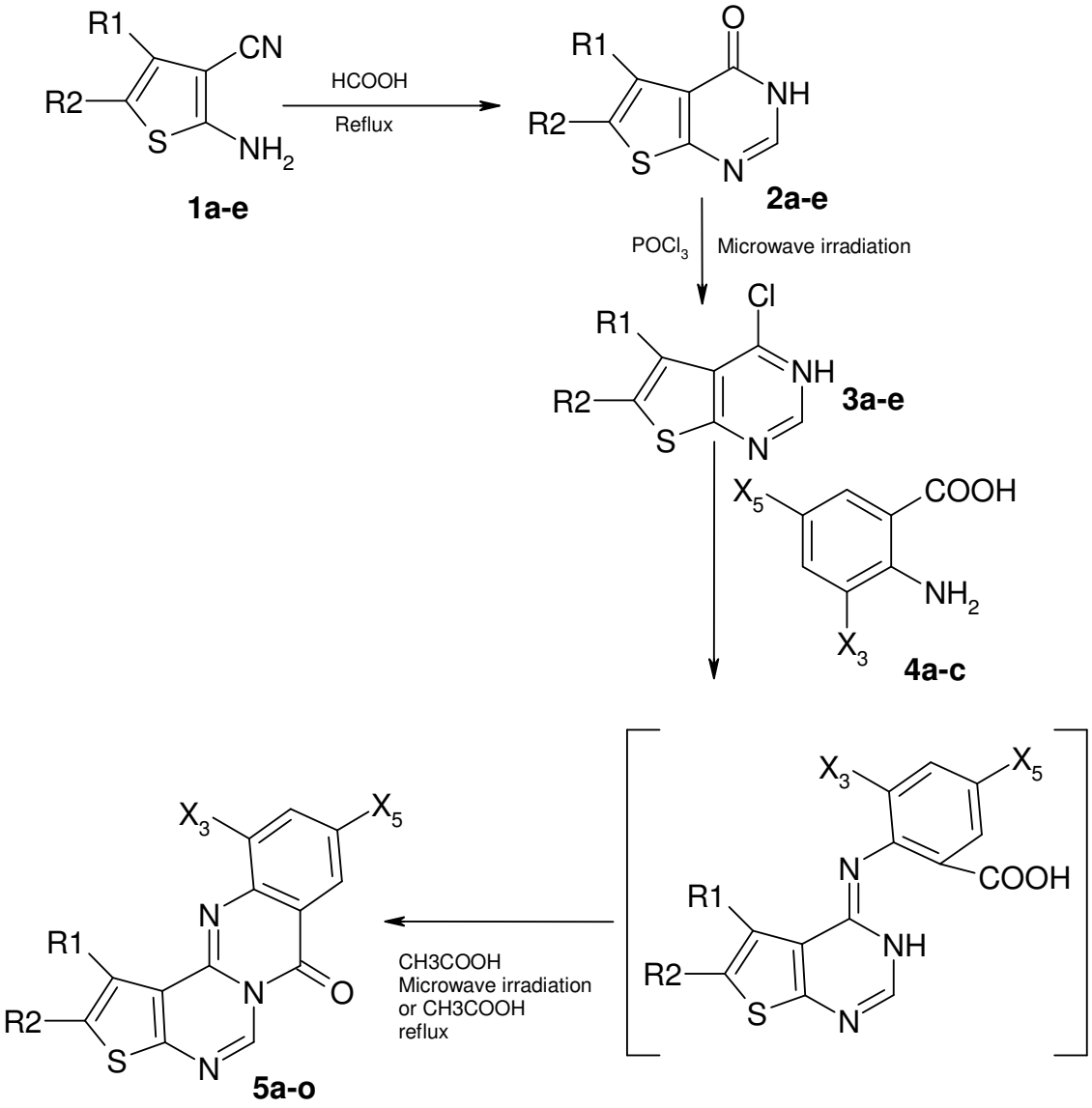
Thieno[2,3-*d*]pyrimidines are an important class of fused heterocycles with a wide range of biological activities such as anti-allergic activity[1-3], analgesic[4-7], anti-inflammatory[4-9], blood sugar lowering[4], CNS depressant[10-12] activities, anticonvulsant[8], antimicrobials[24], local anaesthetic[9], antitussive activity[9], potent PDE 4[13] and PDE 5 inhibitory[14-20] and many more. Rutaecarpine[21] and Luotonine A[22] (Figure 1), the two natural quinazoline fused compounds exhibit a very potent pharmacological activity. In search of new fused heterocyclic compounds of potential pharmaceutical value and in association with our work[23] on the application of microwaves in organic chemistry, we planned to prepare novel tetracyclic 7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-ones **5**, from the reaction between anthranilic acids **4** and thieno[2,3-d]pyrimidines **3**. The synthesis of various congeners took place via a Niementowski condensation, inspired by Alexandre and co-workers[24].

During the next few years the implementation of strict environmental legislation, entails a challenge for chemists that will strive to develop novel products and processes that will provide all the benefits of sustainable development. This requires a novel synthetic approach which will reduce the time and energy intensity of chemical processes and products, decrease or eliminate the dispersion of harmful chemicals in the environment in a way that will enhance industry to meet the challenges of green chemistry[25]. One area where substantial progress has been made is microwave-assisted synthesis[26]. Microwaves

have shown an advantage when processes involve sensitive reagents or products that may decompose under prolonged heating. This technique is particularly attractive for multi-step syntheses[27] and drug discovery[28] where the ability of efficient purification is highly desirable. In this paper we describe the synthesis of the novel 7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one ring system **5** under microwave conditions with the aim of developing a novel and environmentally friendly procedure

Results and Discussion

The synthesis of the 5,6-disubstituted-3*H*-thieno[2,3-*d*]pyrimidin-4-ones **2** was performed by reaction between 2-amino-4,5-disubstituted-thiophene-3-carbonitrile and formic acid[30]. Short exposure (10 min) of a mixture of the **2** with phosphoryl chloride to microwave irradiation led to 4-chloro-3*H*-thieno[2, 3-*d*]pyrimidines **3** in very good yields. The final step of this route involves a Niementowski reaction29 between anthranilic acids **4** and novel 3*H*-thieno[2,3-d]pyrimidin-4-ones **3**. These reactions are carried out either under microwave irradiation or by conventional heating. It is assumed that that the reaction goes via an acid intermediate (Scheme 1) that undergoes intramolecular acyl substitution between a pyrimidine ring nitrogen atom and the acid group to yield compounds **5**. A comparative study between conventional heating (Method A) and microwave irradiation (Method B) revealed that the microwave reactions were a cleaner and higher yielding (Table 1). To our knowledge, no examples of this reaction have yet been reported.


R1
CN
R2
S
NH2
HCOOH
Reflux
1a-e
O
NH
N
2a-e
POCl3
Microwave irradiation
Cl
3a-e
X5
COOH
NH2
X3
4a-c
CH3COOH
Microwave irradiation
or CH3COOH
reflux
5a-o

Scheme 1

Table 1: Physical data of compound 5a-o

Compd	Substitution				Reaction time (min)		Yield (%)		Mp. (^{o}C)
					Method		Method		
	R_1	R_2	X_3	X_5	A	B	A	B	
5a	-(CH2-)$_4$		H	H	90	10	60	95	88-90
5b	p-Cl-phenyl	H	H	H	60	05	70	80	116-118
5c	p-methyl-phenyl	H	H	H	90	06	65	85	220-222
5d	p-methoxy-phenyl	H	H	H	60	07	70	85	120-122
5e	CH3	CH3	H	H	60	05	60	80	130-132
5f	-(CH2-)$_4$		Br	Br	75	08	60	90	118-120
5g	p-Cl-phenyl	H	Br	Br	60	07	65	95	108-110
5h	p-methyl-phenyl	H	Br	Br	90	08	70	90	128-130
5i	p-methoxy-phenyl	H	Br	Br	90	08	70	85	135-137
5j	CH3	CH3	Br	Br	60	05	60	80	178-180
5k	-(CH2-)$_4$		H	Br	75	08	70	95	238-240
5l	p-Cl-phenyl	H	H	Br	60	07	60	85	148-150
5m	p-methyl-phenyl	H	H	Br	60	08	70	90	160-162
5n	p-methoxy-phenyl	H	H	Br	60	08	75	85	122-124
5o	CH3	CH3	H	Br	60	06	60	80	150-152

The IR (KBr) spectra of **5** showed characteristic C=O stretching vibrations in the region 1700-1675cm^{-1}. The C=C and C=N ring stretching vibrations appeared around 1600 and 1570-1520 cm^{-1}. The IR bands due to NH and COOH vibrations were not present in any of the spectra of the compounds **5** which ruled out any intermediates being isolated. Direct cyclization to compounds **5** is also supported by ^{1}H-NMR spectral data and is due to the absence of any NH or OH signals.

Conclusion

We observed that the best procedure for the preparation of 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-ones consists of microwave irradiation (140

W Power input) of a mixture of the 4-chloro-5,6-disubstituted thieno-[2,3-*d*]-pyrimidine with an excess of appropriately substituted anthranilic acids in the presence of acetic acid. The benefits of use microwave irradiation are noticeable and high temperatures, lengthy and tedious conditions of conventional heating are avoided. This work is a further example of the utility of microwave irradiation in organic synthesis. The synthesized compounds are structurally related to terrestrial alkaloids such as Rutaecarpine and Luotonine A_3. Phosphodiesterase inhibitory activity of various analogues is under development and will be described later.

Experimental Section

The microwave irradiated reactions (MWI) were performed in scientific microwave oven RAGA's microwave oven. Melting points were determined in open capillaries using a Thermonik C-PMB-2 precision melting point and boiling point apparatus (Mumbai, India) and are uncorrected. The purity of the compounds was routinely checked by TLC using silica gel-G and the spots were exposed in iodine vapour. IR spectra were recorded using KBr pellets on a Shimadzu 1600 Spectrophotometer from Shimadzu International Incorporation, (vmax, cm^{-1}), ^{1}H-NMR spectra on a Bruker Avance 400 Spectrometer (Bruker AG, Fallanden, Switzerland) at 400 MHz using TMS as internal standard ($CDCl_3$ and chemical shift in δ ppm) and mass spectra (EI-MS) were recorded on a Jeol SX-102 spectrometer (Jeol Ltd.Tokyo, Japan). Elemental analyses were carried out using a Heraeus Carlo Erba 1180 CHN analyzer (from Heraeus Instrument GmbH, Hanau, Germany). All the chemicals were purchased from Aldrich Company Ltd. Dorset (UK).

Synthesis of substituted products of 2-Amino-4, 5-disubstituted-thiophene-3-carbonitrile (1a-e).

These compounds were synthesized from substituted aldehyde and ketones using known procedure described by Gewald[31]. The products **1a-e** was recrystallize from ethanol and obtained in pure form.

Synthesis of substituted products of 5, 6-Disubstituted-3*H*-thieno [2,3-d]pyrimidin -4-one (2a-e).

These compounds were synthesized by heating **1** in formic acid at reflux temperature[30]. The product **2** was obtained in pure form by recrystallization from ethanol.

.

Synthesis of substituted products of 4-chloro-5,6-Disubstituted-3*H*-thieno[2,3-d] pyrimidine (3a-e).

Thienopyrimidin-4-one **2** (4.42 mmole) and $POCl_3$ (6 mL) were irradiated in a microwave oven (140 W power input) until the reaction reached completion (TLC monitoring, 12 min). POCl3 was evaporated in vacuo and the residue was dissolved in EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo to furnish compound **3** as an off-white solid which was used without further purification in the next.

4-Chloro-5,6-disubstituted-3*H*-thieno[2,3-*d*]pyrimidines (**3a**, 85% yield; **3b**, 90% yield; **3c**, 80% yield; **3d**, 85% yield; **3e**, 90% yield;) gave spectroscopic data in accordance with those previously described[30].

Synthesis of substituted anthranilic acids (4a-c).

The mono bromo and di bromo products of anthranilic acid were obtaind using the reported method [32].

Synthesis of 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-ones 5: General procedures

Method A (Classical)
A mixture of **3** (0.61 mmole) and anthranilic acid **4** (3.4 mmole) in CH_3COOH (10 ml) was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure. Recrystallization from ethanol afforded compounds **5**.

Method B (Microwave)
A mixture of **3** (0.61 mmole) and anthranilic acid **4** (3.4 mmole) in CH_3COOH (5mL) was introduced into a pyrex tube. The tube was irradiated in microwave (140 W power input) for 10 min. After reaction solvent was evaporated under reduced pressure. Recrystallization from ethanol afforded compounds **5**.

Spectral data for compounds **5a-o**.

1,2,3,4-Tetrahydro-9*H*-[1]benzothieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-9-one (5a)

IR (KBr) vmax: 1750 (C=O), 1662 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, CDCl3) δ (ppm): 1.83-1.87 (m, 4H), 2.78 (t, 2H), 3.07 (t, 2H), 7.10-8.35 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 23.4, 23.4, 23.8, 24.9, 120.8, 126.6, 126.7, 127.3, 127.6, 129, 133.4, 137.4, 143.7, 144.5, 155.9, 163, 170.6; *m/z* (EI): 307 (M+, 25 %); Anal. Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.12; H, 4.18; N, 13.73%.

1-(4-Chlorophenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5b)

IR (KBr) vmax: 1751 (C=O), 1685 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 7.42-8.50 (m, 1H thiophene + 9H Ar-H); 13C NMR ($CDCl_3$, 75 MHz, δ in ppm) 120.8, 124, 125.3, 125.3, 125.5, 126.6, 126.7, 127.3, 129.3, 129.3, 133.4, 134.3, 134.5, 142.6, 144.5, 148.6, 155.9, 163, 170.6 ; *m/z* (EI): 363 (M^++2, 20 %); Anal. calcd for $C_{19}H_{10}ClN_3OS$: C, 62.73; H, 2.77; N, 11.55. Found: C, 62.25; H, 2.89;N 11.34.

1-(4-Tolyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5c)

IR (KBr) vmax: 1685 (C=O), 1600 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.48 (s,3H, CH3), 7.01-8.49 (m, 1H thiophene + 9H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 120.8, 124, 125.5, 126.6, 126.7, 127.3, 127.4, 127.4, 129.5, 129.5, 131.7, 133.4, 133.4, 142.6, 144.5, 148.6, 155.9, 163, 170.6 ; *m/z* (EI): 343 (M^++2, 18 %); Anal. calcd for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82;, N, 12.24. Found: C, 69.72; H, 3.93; N 12.13.

1-(4-Methoxyphenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5d)

IR (KBr) vmax: 1757 (C=O), 1685 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 3.84 (s,3H, OCH3)7.02-8.85 (m, 1H thiophene + 9H Ar-H); 13C NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 120.8, 124, 125.6, 126.6, 126.7, 127.3, 128.7, 129.7, 129.7, 133.4, 142.6, 144.5, 148.6, 155.9, 160.6, 163, 170.6 ; *m/z* (EI): 359 (M^++2, 20 %); Anal. calcd for $C_{20}H_{13}N_3O_2S$: C, 66.84; H, 3.65; N, 11.69. Found: C, 66.93; H, 3.54; N, 11.78.

1,2-Dimethyl-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5e)

IR (KBr) vmax: 1685 (C=O), 1600 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.40 (s,3H, CH3), 2.50 (s,3H, CH3), 7.10-8.40 (m, 5H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 10.2, 10.4, 120.8, 126.6, 126.7, 127.3, 129, 131.4, 133.4, 136, 144.3, 144.5, 155.9,

163, 170 ; *m/z* (EI): 281 (M^++2, 22 %); Anal. calcd for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.23; H, 3.72; N 14.68.

9,11-Dibromo-1,2,3,4-Tetrahydro-9*H*-[1]benzothieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-9-one (5f)

IR (KBr) vmax: 1762 (C=O), 1683 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 1.79-1.85 (m, 4H), 2.80 (t, 2H), 3.12 (t, 2H), 7.12-8.40 (m, 3H); 13C NMR (CDCl3, 75 MHz, δ in ppm) 23.4, 23.4, 23.8, 24.9, 113.2, 122.0, 125.2, 127.6, 129, 131.3, 137.4, 139.4, 143.7, 150.1, 155.9, 163, 170.6 ; *m/z* (EI): 281 (M^++2, 18 %); Anal. calcd for $C_{17}H_{11}Br_2N_3OS$: C, 43.90; H, 2.38; N, 9.03. Found: C, 43.87; H, 2.42; N, 9.12.

9,11-Dibromo-1,2-Dimethyl-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one(5g)

IR (KBr) vmax: 1762 (C=O) stretching, 1667 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.38 (s,3H, CH3), 2.52 (s,3H, CH3), 7.50-8.35 (m,3H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 10.2, 10.4, 113.2, 122.0, 125.2, 129, 131.3, 131.4, 136, 139.4, 144.3, 150.1, 155.9, 163, 170.6 ; *m/z* (EI): 439 (M^++2, 21 %);Anal. calcd for $C_{15}H_9Br_2N_3OS$: C, 41.03; H, 2.07; N, 9.57. Found: C, 41.22 ; H, 2.32; N, 9.48.

9,11-Dibromo-1-(4-Chlorophenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5h)

IR (KBr) vmax: 1766 (C=O), 1683 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 7.40-8.45 (m, 1H thiophene + 7H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 113.2, 122.0, 124, 125.2, 125.3, 125.3, 125.5, 129.3, 129.3, 131.3, 134.3, 134.5, 139.4, 142.6, 148.6, 150.1, 155.9, 163, 170.6 ; *m/z* (EI): 521 (M^++2, 17 %); Anal. calcd for $C_{19}H_8Br_2ClN_3OS$: C, 43.75; H, 1.55; N, 8.06. Found: C, 43.87; H, 1.49; N 8.17.

9,11-Dibromo-1-(4-Tolyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5i)

IR (KBr) vmax: 1750 (C=O), 1678 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.39 (s,3H, CH3), 7.12-8.45 (m, 1H thiophene + 7H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 113.2, 122, 124, 125.2, 125.5, 127.4, 127.4, 129.5, 129.5, 131.3, 131.7, 133.4, 139.4, 142.6, 148.6, 150.1, 155.9, 163, 170.6 ; *m/z* (EI): 501 (M^++2, 19 %); Anal. calcd for $C_{20}H_{11}Br_2N_3OS$: C, 47.93; H, 2.21; N, 8.38. Found: C, 47.72; H, 2.34; N 8.45.

9,11-Dibromo-1-(4-Methoxyphenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5j)

IR (KBr) vmax: 1760 (C=O), 1678 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 3.75 (s,3H, OCH3), 7.13-8.78 (m, 1H thiophene + 7H Ar-H); 13-C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 113.2, 114.8, 114.8, 122, 124, 125.2, 125.5, 128.7, 129.7, 129.7, 131.3, 139.4, 142.6, 148.6, 150.1, 155.9, 160.6, 163, 170.6 ; *m/z* (EI): 517 (M^++2, 23 %); Anal. calcd for $C_{20}H_{11}Br_2N_3O_2S$: C, 46.45; H, 2.14; N, 8.12. Found: C, 46.23; H, 2.24; N 8.31.

9-Bromo-1,2,3,4-Tetrahydro-9*H*-[1]benzothieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-9-one (5k)

IR (KBr) vmax: 1662 (C=O), 1591 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 1.80-1.89 (m, 4H), 2.84 (t, 2H), 3.02 (t, 2H), 7.02-8.48 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 23.4, 23.4, 23.8, 24.9, 121.7, 123, 124.6, 127.6, 129, 132.3, 136.3, 137.4, 143.5, 143.7, 155.9, 163, 170.6 ; *m/z* (EI): 387 (M^++2, 20 %); Anal. calcd for $C_{17}H_{12}BrN_3OS$: C, 52.86; H, 3.13; N, 10.88. Found: C, 52.98; H, 3.29; N 10.92.

9-Bromo-1,2-Dimethyl-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5l)
IR (KBr) vmax: 1757 (C=O), 1662 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.41 (s,3H, CH3), 2.50 (s,3H, CH3), 8.8-7.08 (m, 4H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 10.2, 10.4, 121.7, 123, 124.6, 129, 131.4, 132.3, 136, 136.3, 143.5, 144.3, 155.9, 163, 170.6 ; *m/z* (EI): 387 (M^++2, 20 %); Anal. calcd for $C_{15}H_{10}BrN_3OS$: C, 50.01; H, 2.80; N, 11.66. Found: C, 50.14; H, 2.98; N 11.45.

9-Bromo-1-(4-Chloro-phenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5m)

IR (KBr) vmax: 1757 (C=O), 1676 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 7.12-8.62 (m, 1H thiophene + 8H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 121.7, 123, 124, 124.6, 125.3, 125.3, 125.5, 129.3, 129.3, 132.3, 134.3, 134.5, 136.3, 142.6, 143.5, 148.6, 155.9, 163, 170.6 ; *m/z* (EI): 443 (M^++2, 18 %); Anal. calcd for $C_{19}H_9BrClN_3OS$: C, 51.55; H, 2.05; N, 9.49. Found: C, 51.28; H, 2.28; N, 9.67.

9-Bromo-1-(4-Tolyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5n)
IR (KBr) vmax: 1757 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 2.41 (s,3H, CH3), 7.18-8.52 (m, 1H thiophene + 8H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 121.7, 123, 124, 124.6, 125.5, 127.4, 127.4, 129.5, 129.5, 131.7, 132.3,

133.4, 136.3, 142.6, 143.5, 148.6, 155.9, 163, 170.6 ; *m/z* (EI): 423 (M^++2, 21 %); Anal. calcd for $C_{20}H_{12}BrN_3OS$: C, 56.88; H, 2.86; N, 9.95. Found: C, 56.67; H, 2.97; N 9.78.

9-Bromo-1-(4-Methoxyphenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]quinazolin-7-one (5o)

IR (KBr) vmax: 1768 (C=O), 1682 (C=N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, δ in ppm) 3.78 (s,3H, OCH3), 7.18-8.83 (m, 1H thiophene + 8H Ar-H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 121.7, 123, 124, 124.6, 125.5, 128.7, 129.7, 129.7, 132.3, 136.3, 142.6, 143.5, 148.6, 155.9, 160.6, 163, 170.6 ; *m/z* (EI): 439 (M^++2, 17 %); Anal. calcd for $C_{20}H_{12}BrN_3O_2S$: C, 54.81; H, 2.76; N, 9.59. Found: C, 54.97; H, 2.85; N, 9.78.

Acknowledgements

One of the authors (SSL) is thankful to Ms. Sweety Laddha for her encouragement during the project. They wish to thank SAIF,CDRI Lucknow, India for recording spectra, Head, Department of Pharmaceutical Sciences, Birla Institute of Technology, Ranchi and Principal, R. C. Patel College of Pharmacy, Shirpur, India, for providing facilities.

Communication Address:
Mr. Sachin S. Laddha,
Assistant Professor, SVBs College of Pharmacy, Sonarpada,
Off Kalyan Shill Highway, Phase II, MIDC,
Dombivali(E), Dist: Thane 421203 MS,
India. E-mail: pinkumanno@rediffmail.com

References

1. Kretzschnar, K.; Gabau, G. Ger,(East). Pat., 272, 090, 1989; *Chem. Abstr.* **1990**, 112, 216953.
2. Kretzschnar, K.; Gabau, G. Ger,(East). Pat., 272,087, 1989; *Chem. Abstr.* **1990,** 112, 132206.
3. Temple Jr. D. L. Ger. Offen. 324698, 1979; *Chem. Abstr.* **1979**, 91, 74644.
4. Devani, M. B.; Shishoo, C. J.; Pathak, U. S.; Parikh, S. H.; Shah, G. J.; Padhya, A. C. *J. Pharm. Sci.,* **1976**, 65, 660.
5. Sauter, F. Ger. Offen., 2, 104, 435, 1971; *Chem. Abstr.* **1971**, 75, 140883.

6. Tahara, T.; Hamasak, T. Japan Kokai, 75140487, 1975; *Chem. Abstr.* **1976**, 85, 21428.
7. Monique, P.; Duc, M.I.; Francois, C.; Guy, N. *Eur. J. Med. Chem. Ther.* **1984**, 19(5), 420.
8. Devani, M. B.; Shishoo, C. J.; Pathak, U. S.; Parikh, S. H.; Radhakrishnan, A. V.; Padhya, A. C. *Indian. J. Chem.* **1976**, 14, 357.
9. Sauter, A.; Gerhard, S. *Arch. Pharm.* **1976,** 101, 309.
10. Manhas, M. S.; Sharma, S. D.; Sharma, S. G. *J. Med. Chem.* **1972,** 15, 106.
11. Nakanishi, M.; Shiroki, M. Jap. Pat. 7,242, 271, 1972; *Chem. Abstr.* **1976,**85, 160152.
12. Kulshreshtha, M. J.; Bhatt, S.; Madhuri, P.; Khanna, N. M. *J. Indian Chem. Soc.* **1981,** 58(10), 982.
13. Kim, D.-K.; Lee, J.Y.; Ryu, D.H.; Lee, N.K.; Lee, S.H.; Kim, N.-H.; Kim, J.-S.; Ryu, J.H.; Choi, J.-Y.; Im, G-J.; Choi, W.-S.; Kim, T.K.; Cha, H. PCT Int. Appl. WO 01, 60825,2001; *Chem. Abstr.* **2001,**135, 195571.
14. Oota, T.; Kawashima, Y.; Hatayama, K. Jpn. Kokai Tokkyo Koho JP 07330777, 1995; *Chem. Abstr.* **1995,** 124, 289561.
15. Oota, T.; Kawashima, Y.; Hatayama, K. Jpn. Kokai Tokkyo Koho JP 07267961, 1995; *Chem. Abstr.* **1995,** 124, 146193.
16. Jonas, R.; Kluxen, F.-W.; Schelling, P.; Christadler, M. Ger. Offen., DE 19752952, 1999; *Chem. Abstr.* **1999,** 131, 19019.
17. Jonas, R.; Schelling, P.; Kluxen, F.-W.; Christadler, M.; PCT Int. Appl. WO 9955708, 1999; *Chem. Abstr.* **1999,** 131, 310646.
18. Rochus, J.; Eiermann, V.; Bernotat-Danielowski, S. Ger. Offen., DE 19943815, 2001; *Chem. Abstr.* **2001,**134, 242642.
19. Eiermann, V.; Jonas, R. Ger. Offen., DE 19944604, 2001; *Chem. Abstr.* **2001,** 134, 237491.
20. Jonas, R.; Schelling, P.; Christadler, M.; Beier, N. PCT Int. Appl. WO 020064, 2002; *Chem. Abstr.* **2002,** 136, 85819.
21. Yang, L.-M.; Chen, C.-F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, 5, 465–468, and references therein.
22. Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, 46, 541–546.
23. a) Laddha, S.S.; Wadodkar, S.G.; Meghal, S.P. *Arkivoc* **2006**, *xi*, 1-20; b)Laddha, S.S.; Bhatnagar, S.P. *Phosphorous, Sulphur and Silicon* (Accepted); Laddha S.S.; Bhatnagar, S.P. *Arkivoc* (Accepted)
24. Alexandre,F-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T.; *Tetrahedron* 59 (2003) 1413–1419.
25. Xie, W.; Jin, Y.; Wang, P.G. *Chemtech.* **1999,** 29, 23–29.
26. Varma, R.S. *Green Chem.* **1999,** 1 , 43–55.
27. Besson, T.; Guillard, J.; Rees, C. W. *Tetrahedron Lett.* **2000**, 41, 1027–1030.

28. Wathey, B.; Tierney, J.; Lidstro¨m, P.; Westman, J. *Drug Discov. Today* **2002**, 7, 373–380.
29. von Niementowski, S. *J. Prakt. Chem.* **1895**, 51, 564–572
30. Murumkar, P.R. M-Pharm. Thesis submitted to North Maharastra University, Jalgaon, **2004.**
31. Gewald, K. *Chem. Ber.*, **1965,** 98, 3571.
32. Bogert, C.; Hund, G. *J. Chem. Soc.* **1905,** 27, 1484.