Int. J. Chem. Sci. : 3 (3), 2005, 469–474

SYNTHESIS OF SOME NOVEL BIS THIENO [2,3–d] PYRIMIDINES AND RELATED HETEROCYCLES

R. O. BORA[a], I. S. RATHOD[b], S. S. TOSHNIWAL[c] and M. FAROOQUI[d]

[a] Wockhardt Research Centre, AURANGABAD – 431210 (MS) INDIA.
[b] L.M. College of Pharmacy, AHMEDABAD – 385009 (Guj.) INDIA.
[c*] Y.B. Chavan College of Pharmacy, Rauza Bag, AURANGABAD – 431001 (MS) INDIA.
E.Mail : toshniwal_ss@yahoo.com
[d] Aurangabad College for Women, AURANGABAD – 431001 (MS) INDIA.

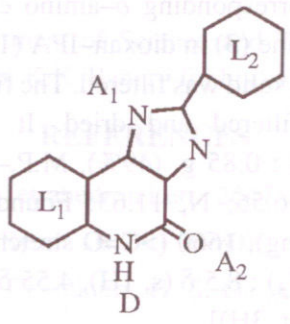
ABSTRACT

A series of novel symmetric and asymmetric bis–thienopyrimidines and related heterocycles have been synthesized. The shtructures of the synthetized compounds elucidated by spectral and elemental analysis.

Key words : BzR–Benzodiazepine receptors, *i.p.*– Intra peritoneal, CMC–Carboxy Methyl Cellulose.

INTRODUCTION

Thieno[2,3,–d] pyrimidines have been found to exhibit a variety of biological activities viz., CNS depressant, anticonvulsant, analgesic, anti–pyretic, anti–bacterial, antifungal, anti–viral, anti–tumor etc.[1, 2] Thieno [2,3–d] pyrimidines are the isosters of quinazolines and found to be equally important biologically.[3, 4] After the discovery of BzR, structurally unique classes of ligands have been identified, which exhibit the action varying from CNS depressant to producing convulsions.[5] A necessary criteria for high affinity binding of ligands to BzR is the ability of these molecules to assume a planar or psuedoplanar topography. There exists a variety of such nonbenzodiazepine ligands that bind in nanomolar range to BzR.[6] Lucia *et al.*[7] have



(A)

reported the pharamacophoric model of a ligand for BzR binding[7]. It is based on 6, 6, 5–tricyclic heterocyclic compounds in which some essential and optional pharamacophoric descriptors are identified as shown below.

The essential pharmacophoric descriptors are thought to be

(i) Two lipophilic substituents $\mathbf{L_1}$ and $\mathbf{L_2}$

(ii) Proton acceptor atoms $\mathbf{A_2}$

Optional sites, which are not necessary for receptor ligand interaction but can affect the potency of a ligand are –

(i) Proton acceptor site $\mathbf{A_1}$

(ii) Proton donor site **D**

Based on the above reports, it was proposed to synthesize substituted Thieno [2,3–d] pyrimidines and related heterocycles.[15]

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (λmax in cm^{-1}) were recorded on a Perkin–Elmer 841 IR spectrophotometer and ^1H NMR spectra on a JNM–PMX 60 using TMS as internal standard.

Synthesis of 4–chloro–5, 6–dimethylthieno [2,3–d] pyrimidine (3)

To a solution of 4–oxo–5,6–dimethyl thieno [2,3–d] pyrimidine (**2**) (5.0 g; 0.025M) in phosphorous oxychloride (50.0 mL) in dry round bottom flask was added few drops of N, N–diethylaniline. It was refluxed for 5 hr. Phosphorous oxychloride was distilled off and then poured into crushed ice and neutralized with saturated solution of sodium bicarbonate. The solid separated was filtered suck dried under vaccum. (Yield– 4.0 g. (85%), m.p.–103–105°C.)

General procedure– Synthesis of 4–(3' carbethoxy–4', 5'–substituted thienyl) amino–5,6–dimethyl thieno [2,3–d] pyrimidine (7a)

An equimolar solution of corresponding *o*–amino esters (**1**) and 4–chloro–5,6–disubstituted thieno [2,3–d] pyrimidine (**3**) in dioxan–IPA (1:1) was refluxed for 24–30 hr. It was allowed to cool and separated solid was filtered. The filtrate was poured onto ice–water mixture; resultant solid was filtered and dried. It was then recrystallised using chloroform–ethanol (1:1). [Yield : 0.85 g. (49%), M.P.–215–217°C, Elemental analysis calcd. for $C_{17}H_{19}N_3O_2S_2$: C, 56.56; N, 11.63: Found C,57.32; H, 5.51; N, 11.64., IR(KBr)cm^{-1}: 3220 (NH stretching), 1660 (>C=O stretching). 1580 (NH bending). Mass (m/z) : 362 M^+), ^1H NMR ($CDCl_3$) : 8.5 δ (s, 1H), 4.55 δ (s, 1H), 4.2–4.4 δ (q, 2H), 2.7 δ (s, 6H), 2.43 δ (s, 6H), 1.3–1.5 δ (t, 3H)].

Synthesis of 5,6,9,10–tetramethyl–bis thieno [2.3 : 4,5] [2,3–d) pyrimidol [1,6–pyrimidin–4–(3H)–one (8a)

To a solution of (**7a**) (0.85 g., 0.002M in DMF) was added catalytic anhydrous potassium carbonate and refluxed it for 6 hr. Progress of the reaction was monitored by TLC. The reaction mixture was poured onto crushed ice and resultant solid was filtered, dried and recrystallised from chloroform. [Yield– 0.35 g. (35%), M.P.–268–270 °C, Elemental analysis calcd. for $C_{15}H_{13}N_3OS_2$: % C, 57.14; H, 4.12; N, 13.33: Found % C, 57.64; N, 13.52. IR (KBr) cm^{-1} :2940, 2860 (CH strech), 1710 (>C=O), Mass (m/z): 316 (M^+), ^1H NMR($CDCl_3$) : 8.5 δ (s, 1H), 2,79 δ (s, 6H), 2.43 δ (s, 6H)].

Synthesis of 4–(3'–carbethoxy–4,5,6,7–tetrahydrobenzo[b]–thienyl) amino–5,6–dimethyl thieno [2,3–d] Pyrimidine (7b)

Prepared from (**2a**) (2.0 g, 0.01M) and 4–chlorothieno [2,3–d] pyrimidine (**3**) (2.0 g, 0.01M). [Yield: 0.8 g. (40%), M.P.: 220–221°C, Elemental analysis calcd for $C_{19}H_{21}N_3O_2S_2$ % C, 58.87; H, 5.42; N, 10.85: Found % C, 59.71; H, 5.59; N, 10.69, IR (KBr)cm^{-1}: 3220 (NH strech), 2950, 2840 (CH strech), 1670 (>C=O strech), 1585 (NH bending), Mass (m/z) : 388(M^+), ^1H NMR ($CDCl_3$) : 8.5 δ (s, 1H), 4.55 δ (s, 1H), 4.2–4.4 δ (q, 4H), 2.7 δ (s, 3H), 2.7–2.4 (m, 4H), 2.35 (s, 3H), 1.45–2.35 (m, 4H), 1.3–1.5 δ (t, 3H).

Synthesis of 5,6,7,8–tetrahydrobenzo [b]–11,12–dimethyl–bis–thieno [2'3':4,5] pyrimido [1,6–a] pyrimidin–4(3H)–one (8b)

Prepared from (**7b**) (1.0 g, 0.002M) similar to procedure described in (**8a**). [Yield: 0.45 g. (45%), M.P.: 210 °C, Elemental analysis calcd for $C_{17}H_{15}N_3OS_2$ % C, 56.89; H, 4.39; N,12.31: Found % C, 56.81; H,4.51; N, 12.25., IR(KBr)cm^{-1} : 2950, 2840 (CH strech), 1710 (>C=O strech), Mass (m/z): 342(M^+), ^1H NMR($CDCl_3$): 8.5 δ (s, 1H), 2.79 δ (s, 6H), 2.7–2.4 (m, 4H), 1.45–2.35 (m, 4H)].

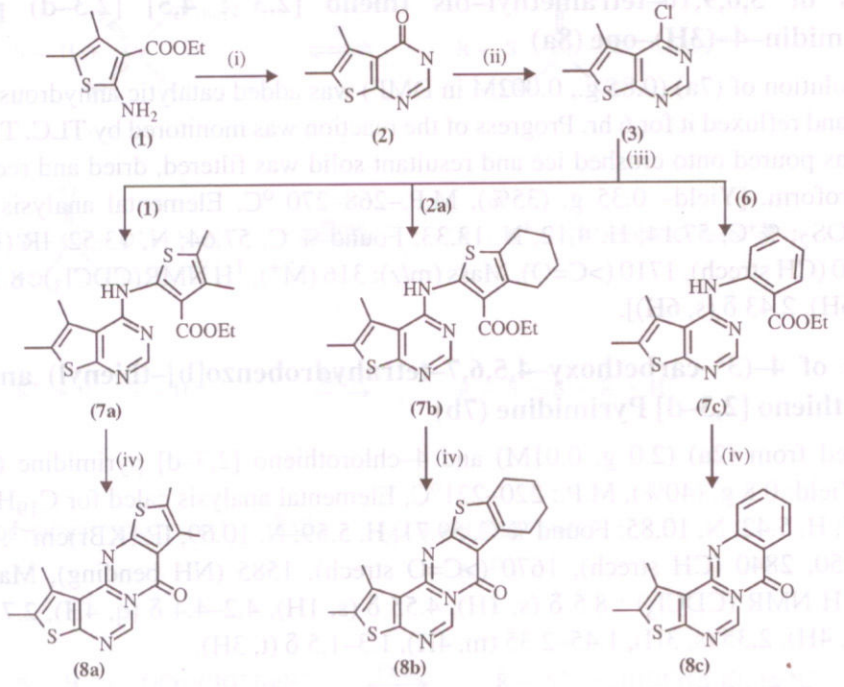
Synthesis of 4(2'–carbomethoxy–phenyl)–5,6–dimethyl thieno [2,3–d] pyrimidine (7c).

Prepared from methyl anthranilated (**4**) (1.5 g., 0.01M) and 4–chloro 5,6–dimethylthieno [2,3–d] pyrimidine (**3**) (1.5 g x 0.0075M). [Yield: 0.75 g. (42.5%), M.P.:170°C, Elemental analysis calcd for $C_{16}H_{15}N_3O_2S$ % C, 61.34; H, 4.79; N, 13.41: Found % C, 61.42; H, 4.86; N,13.47., IR (KBr)cm^{-1} : 3260(NH strech), 2960, 2930 (CH strech), 1700(>C=O strech), 1600 (NH bending), Mass(m/z): 314(M^+), ^1H NMR($CDCl_3$) : 8.5 δ (s, 1H), 8.1–7.5 δ (m, 4H), 4.55 δ (s, 1H), 3.8 δ (s, 3H), 2.79 δ (s, 3H), 2.43 (s, 3H)].

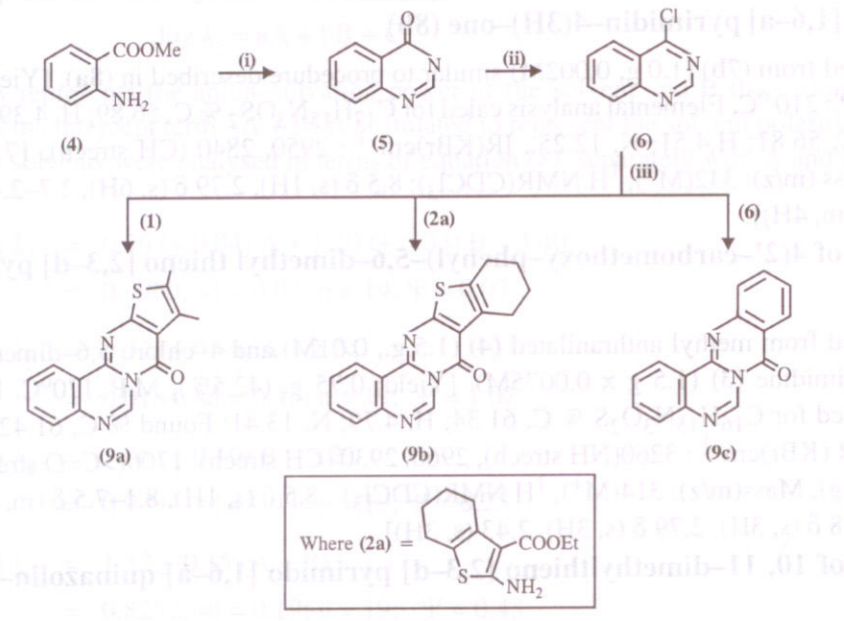
Synthesis of 10, 11–dimethylthieno [2,3–d] pyrimido [1,6–a] quinazolin–4–(3H)–one (8c)

Prepared from (**7c**) (1.0 g, 0.0035M) similar to the procedure described for (**7a**). [Yield: 0.5 g. (50%), M.P.: 173°C, Elemental analysis calcd for $C_{15}H_{11}N_3OS$ %C, 64.05; H, 3.91; N,

Scheme-I



Scheme-II



Reagents and conditions : (i) $HCONH_2$/reflux/4hr, (ii) $POCl_2$/reflux/6hr, (iii) IPA-Dioxan/reflux/8 hr (iv) DMF/K_2CO_2/reflux/24 hr

14.94: Found % C, 64.15; H, 3.97; N, 14.99; IR(KBr)cm^{-1}: 2960, 2930(CH strech), 1700 (>C=O strech), Mass (m/z): 282(M^+), ^{1}H NMR($CDCl_3$): 8.5 δ (s, 1H), 8.1–7.5 δ (m, 4H), 2.7 δ(s, 6H).

Synthesis of quinazolin–4(3H)–one (7b)

Prepared from methyl anthranilate (10.0 g, 0.66M) similar to that of (**2**) [Yield: 7.5 gm (80%), M.P.: 223–225°C]

Synthesis of 4–chloro quinazoline (6)

To a solution of 5 (5.0 g., 0.025M) in phosphorous oxychlorie (50.0 mL) in dry round bottom flask was added few drops of conc. HCl. It was refluxed for 6 hr. Phosphorous oxychloride was distilled off and then poured onto crushe ice and neutralized with 50% solution of sodium hydroxide. Aqueous layer was extracted with dichloromethane (50.0 mL x 2). Combined organic layer was dried over Na_2SO_4 and evaporated under vacuum, yielding liquid product. [Yield:1.25 g (25%)].

Synthesis of 4,5–dimethylthieno [2'3':4,5] pyrimido [1,2–c]quinazolin–4(3H)–one (9a)

Prepared from (**1**) (2.0 g, 0.01M) and 4–chloroquinazolin (**6**) (2.0 g, 0.12M) similar to the procedure described for (**7a**). [Yield: 0.65 (65%), M.P.: 175–177°C, Elemental analysis calcd for $C_{15}H_{11}N_3OS$% C, 64.05; H, 3.91; N, 14.94: Found % C, 64.25; H, 3.99; N, 14.86, IR(KBr)cm^{-1} : 3000, 2950 (CH strech), 1705 (>C=O strech), Mass(m/z): 282(M^+), NMR ($CDCl_3$) : 8.75 δ (s, 1H), 8.2–7.6 δ (m, 4H), 2.79 δ (s, 6H)].

Synthesis of 5,6,7,8–tetrahydrobenzo[b]–thieno[2',3':4,5] pyrimido[1,2–c] quinazolin–4(3H)–one (9b)

Prepared from (**2a**) (2.24 g, 0.01M) and 4–chloroquinazoline(6) (1.64 g, 0.01M) similar to the procedure described for (**7a**). [Yield: 1.2 g (73%), M.P.: 280°C, Elemental analysis calcd for $C_{17}H_{13}N_3OS$ % C, 66.44; H, 4.23; N, 13.68 : Found % C, 66.57; H. 4.37; N, 13.76. IR (KBr)cm^{-1} : 2960, 2850 (CH strech), 1669 (>C=O strech), Mass(m/z) : 308 (M^+), ^{1}H NMR ($CDCl_3$): 8.75 δ (s, 1H), 8.2–7.6 δ (m, 4H), 2.7–2.4 (m, 4H), 1.45–2.35 (m, 4H)].

Synthesis of [3,2–b] bis–quinazolin–4(3H)–one (9c)

Prepared from methyl anthranilate (1.0 mL, 0.006 M) and 4–chloroqunazolin (**6**) (1.0 g, 0.006M) similar to procedure described for (**7a**). [Yield: 0.5 g. (50%), M.P.: 185–187°C, Elemental analysis calcd for $C_{15}H_9N_3O$ % C, 72.87; H, 3.64; N, 17.00: Found % C, 72.96; H, 3.76; N, 17.10., IR (KBr)cm^{-1} : 2950, 2850 (CH strech), 1700 (>C=O strech)., Mass(m/z): 248(M^+)., ^{1}H NMR ($CDCl_3$): 8.9 δ(s, 1H), 8.6–8.3 δ (m, 4H), 8.2–7.6 δ (m, 4H)].

RESULTS AND DISCUSSION

The target compounds (**7a–7c**), (**8a–8c**) and (**9a–9c**) were synthesized through the route depicted in the **Scheme–I** and **II**. 2–amino–3–carbethoxy–4,5–dimethyl thiophene (**1**) was synthesized by Gewald reaction[8] followed by treatment with formamide[9] yielded substituted thieno[2,3–d] pyrimidine (**2**) was then chlorinated using phosphorous oxychloride to get 4–chloro substituted [2,3–d] pyrimidine[10, 11](**3**). Nucleophilic displacement of chloro group by *o*–amino esters yielded open chain compounds (**7a–7c**). By refluxing former compounds in DMF and K_2CO_3 gave the target compounds (**8a–8c**). The structures of the synthesized compounds were confirmed on the basis of Mass, ^{1}H NMR, IR and elemental analysis.

ACKNOWLEDGEMENT

The authors are thankful to Dr. C. J. Shishoo, Principal, L.M. College of Pharmacy, Ahmedabad for encouragement and research facility.

REFERENCES

1. Sauter R. Gerhard, *Arch. Pharm.*, **309**, 101 (1970).
2. V. Shirsath, *M. Pharm. Dissertation* Guj. Univ. India (1995).
3. M. J. Kulshreshtha *J. Chem.*, **58**, 982 (1981).
4. M. Manhas, *J. Med. Chem.*, **15**, 106 (1972).
5. F. William. *Principles of Medicinal Chemistry*, **4th Edition**, (1995) pp. 167–174.
6. L. T. Mark, *J. Med. Chem.*, **30**, 456 (1987).
7. Lucia et al., *J. Med. Chem.*, **39**, 2844 (1996).
8. K. Gewald, *Chem. Berg.*, **99**, 94 (1965).
9. F. Sauter, *Mantasch Chem.*, **104**, 1593 (1973).
10. A. Orjales and R. Rodes. *J. Med. Chem.*,40, (1997).
11. A. V. Nargund, *M. Pharm. Dissertation.* Guj. Univ. India (1983).
12. U. K. Seth. *Selected Topics in Experimental Pharmacology*, 125, (1984).
13. D. R. Laurence, *Evaluation of Drug Activities Pharmacometrics*, 272 (1964).
14. D. M. Bailey, *Annual Reports In Med. Chem.*, **19**, 321 (1984).
15. Haefly W. *Adv. Drug Research*, **14**, 165–238 (1990).

Accepted : 26.8.2005