Benzoxazine, Quinazoline and Azole Moieties

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Síntesis de nuevas tienopirimidinas con fragmentos benzoxazina, quinazolina y azol

Síntesi de noves tienopirimidines amb fragments benzoxazina, quinazolina i azole

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RESUMEN

La reacción del cloruro de tienopirimidinoílo 3 con 2-aminociclohexanotiofeno-3-carboxamida 4 rinde el derivado de tienopirimidina 5, producto que experimenta ciclodeshidratación para dar la tienopirimidina 6. Se consigue sintetizar los derivados de benzamidazol 8 y benzoxazol 10 por condensación del cloruro de tienopirimidinoílo 3 y *o*-fenilendiamina o *o*-aminofenol seguida de ciclación. La reacción de la 4-tio-6-metil-2-(*p*-metoxifenil)-5-acetilpirimidina 1 y la *N*-(o-carboxifenil)cloroacetamida 11 da el derivado de pirimidina 12, que cicla rindiendo la benzoxazina 13. El compuesto 13 se transforma en los derivados de quinazolina 14a-c y 16. La reacción de 13 con semicarbazida rinde la triazoloquinazolina 18.

Palabras clave: **Cloruro de tienopirimidinoílo. Tienopirimidina. Benzamidazol. Benzoxazol. Pirimidina. Benzoxazina.**

SUMMARY

Reaction of thienopyrimidinoyl chloride 3 with 2-aminocyclohexanothiophene-3-carboxamide 4 yielded thienopyrimidine derivative 5 that undergoes cyclodehydration to afford thienopyrimidine 6. The synthesis of benzamidazole 8 and benzoxazole 10 derivatives was achieved by condensation of thienopyrimidinoyl chloride 3 and *o*-phenylenediamine / *o*-aminophenol followed by cyclization. Reaction of 4-thio-6-methyl-2-(*p*-methoxyphenyl)-5-acetylpyrimidine 1 and *N*(o-carboxyphenyl) chloroacetamide 11 yielded pyrimidine derivative 12 that cyclized to benzoxazine 13. Compound 13 was transformed to quinazoline derivatives 14a-c and 16. Reaction of 13 with semicarbazide yielded triazoloquinazoline 18.

Key words: **Thienopyrimidinoyl chloride. Thienopyrimidine. Benzamidazole. Benzoxazole. Pyrimidine. Benzoxazine.**

RESUM

La reacció del clorur de tienopirimidinoïl 3 amb 2-aminociclohexantiofen-3-carboxamida 4 rendeix el derivat de tienopirimidina 5, producte que experimenta ciclodeshidratació per donar la tienopirimidina 6. S'assoleix la síntesi dels derivats de benzamidazole 8 i benzoxazole 10 per condensació del clorur de tienopirimidinoïl 3 i *o*-fenilendiamina o *o*-aminofenol seguida de ciclització. La reacció de la 4-tio-6-metil-2-(*p*-metoxifenil)-5-acetilpirimidina 1 i la *N*-(o-carboxifenil)cloroacetamida 11 dóna el derivat de pirimidina 12, que ciclitza a la benzoxazina 13. El compost 13 es transforma en els derivats de quinazolina 14a-c i 16. La reacció de 13 amb semicarbazida rendeix la triazoloquinazolina 18.

Mots clau: **Clorur de tienopirimidinoïl. Tienopirimidina. Benzamidazole. Benzoxazole. Pirimidina. Benzoxazina.**

INTRODUCTION

Numerous publications describe the synthesis of condensed pyrimidines possessing a variety of pharmacological activities such as anticonvulsant[1], anti-inflammatory[2], Bactericidal[3], fungicidal[4] and antifertility activities[5]. The present study was directed to synthesis of several novel thienopyrimidines with heterocyclic moieties from 5-acetyl-4-mercaptopyrimidines[6, 7].

RESULTS AND DISCUSSION

The readily available 4-Thio-6-methyl-2-(p-methoxyphenyl)-5-acetyl-pyrimidine **1**, seemed to be a good starting material containing the suitably located functionality for direct conversion into the thiophene ring with a suitable reagent. Thus Alkylation of compound **1** using chloroacetic acid gives carboxymethylmercaptopyrimidine **2** which react with thionyl chloride producing the corresponding acid chloride **3** (**Scheme 1**).

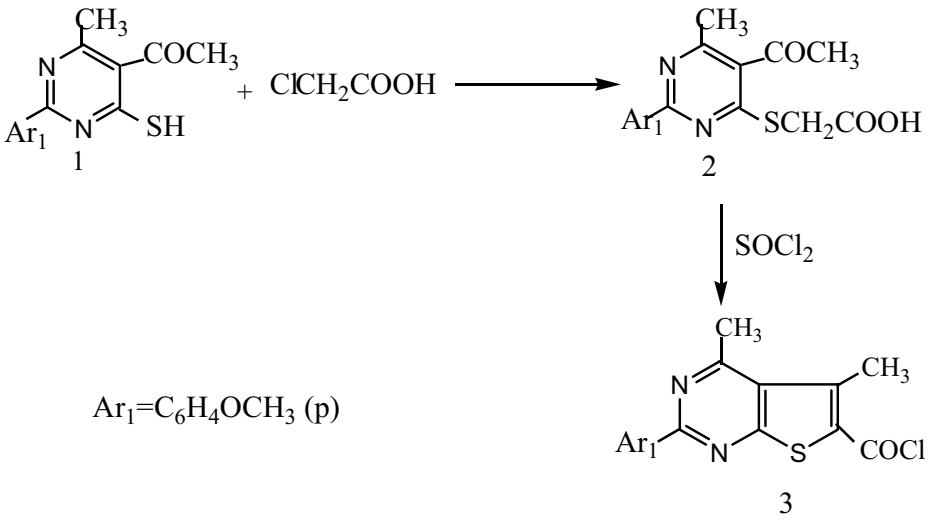
The reaction of thienopyrimidinoyl chloride **3** with ortho functionalized amine derivative produce anilide that used for further heterocyclization. Thus, when thienopyrimidinoyl chloride **3** was allowed to react with 2-aminocyclohexanothiophene-3-carboxamide **4** produced thienopyrimidine derivative **5**, basic heterocyclization of **5** resulted in cyclization via the attack of amino function of amide to the carbonyl group followed by dehydration affording thienopyrimidinylthienopyrimidine **6** (**Scheme 2**).

Thus, condensation of acid chloride **3** with orthophenylenediamine produced the corresponding anilide **7**. Refluxing anilide derivative **7** resulted in intramolecular cyclodehydration affording benzimidazolylthienopyrimidine **8** (**Scheme 3**).

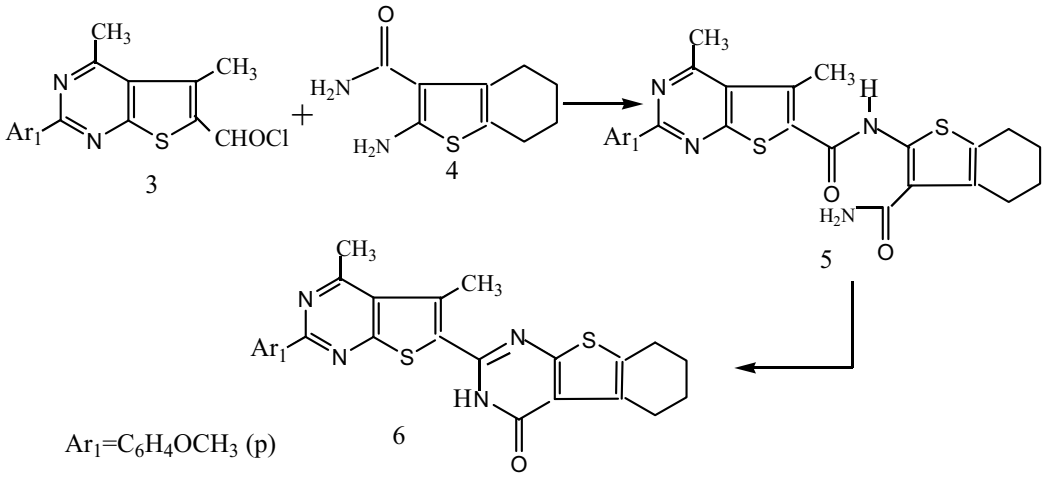
When *o*-aminophenol was allowed to react with acid chloride **3** at room temperature produced anilide derivative **9**. Cyclization of compound **9** was achieved by refluxing in acetic anhydride to produce **10** (**Scheme 4**).

The reaction of 4-mercaptopyrimidine derivative **1** with N(*o*-carboxyphenyl)-chloroacetamide **11** in the presence of trimethylamine (TMA) produced anilide **12**. Refluxing compound **12** in acetic anhydride resulted in intramolecular cyclization affording thienopyrimidine in addition to the formation of benzoxazinyl ring affording **13** (**Scheme 5**).

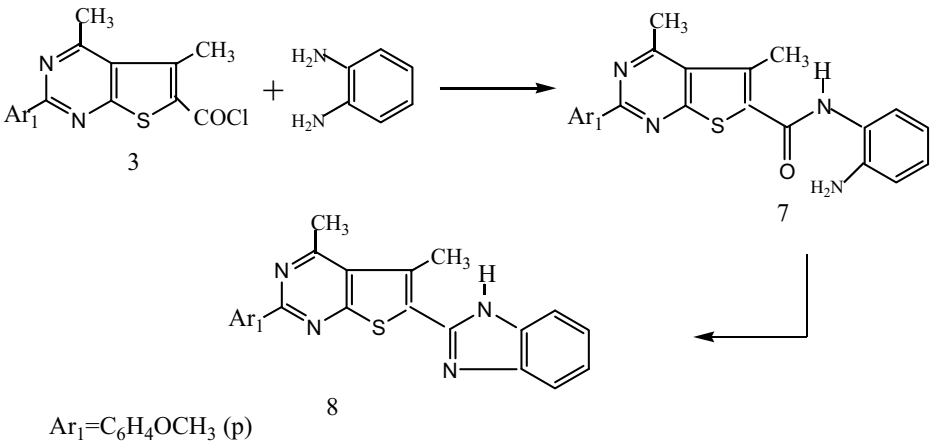
The aminolysis of benzoxazine **13** with primary amines and hydrazine hydrate resulting ring transformation affording 2-Thieno-[2,3-d]pyrimidinoyl-3-aryl-4(3H)quinazolinone **14a,b** while, hydrazinolysis of **13** using hydrazine hydrate yielded N-aminoquinazolinone **14c** (**Scheme 6**).



Schema 1.

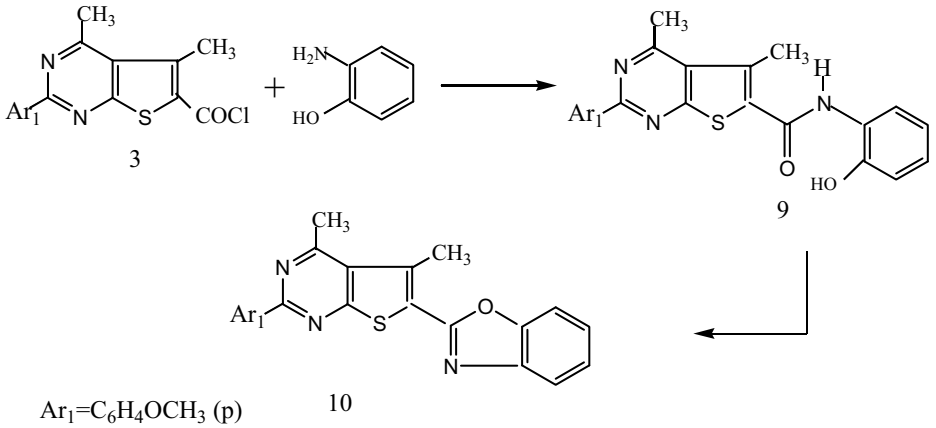


Schema 2.



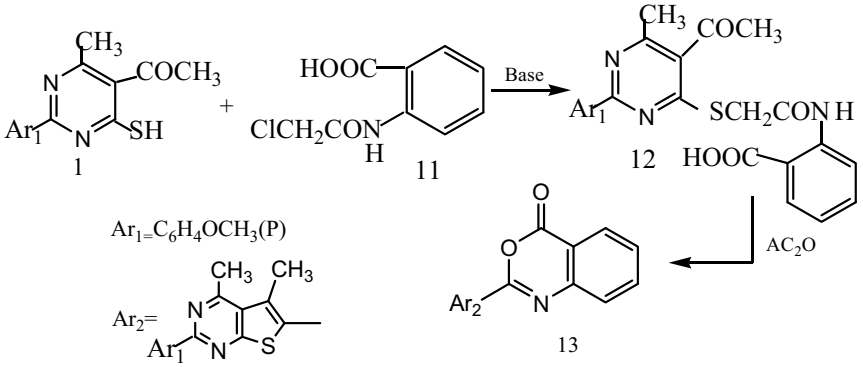
$Ar_1=C_6H_4OCH_3$ (p)

Schema 3.

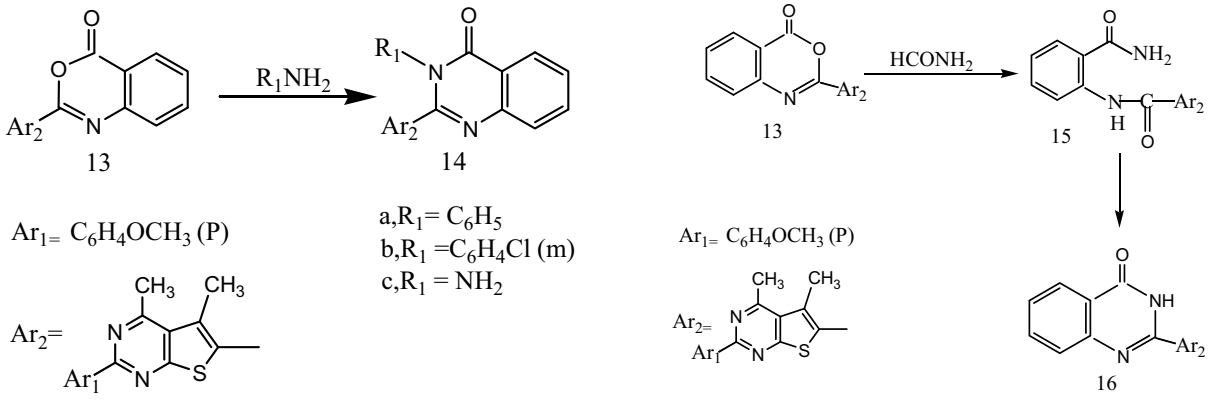


$Ar_1=C_6H_4OCH_3$ (p)

Schema 4.



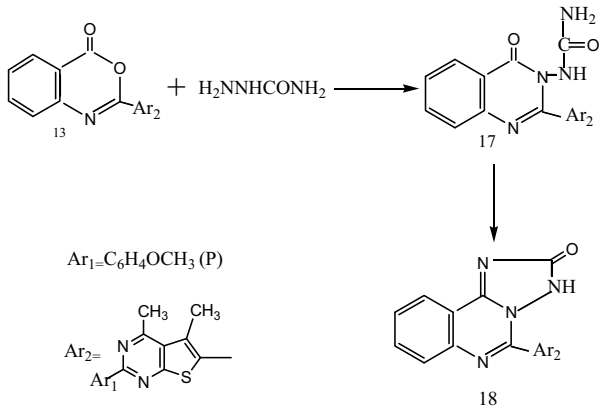
Schema 5.



Schema 6.

Schema 7.

Compound **13** undergoes amonolysis using formamide followed by intramolecular cyclocondensation to produce quinazolinone **16** (**Scheme 7**).
Refluxing compound **13** and semicarbazide produced triazoloquinazoline **18**.
The formation of **18** from benzoxazine **13** and semicarbazide may be proceed via the formation of urea derivative **17** followed by interamolecular cyclo-dehydration affording **18** (**Scheme 8**).



Schema 8.

EXPERIMENTAL

General procedures

All melting points are uncorrected and were recorded on Büchi 510 apparatus. IR spectra were recorded as KBr disks on a perkin- Elmer 383- Spectrometer and FTIR spectrometer Nicollet, impact 400. ^{1}H NMR was obtained a Bruker Ac 200f and Ac 250, DRX400instrument at room temperature using TMS as internal standard. Micro analysis were carried out at micro analytical center, Cairo University, Egypt, National Research Center and Friedrich – Schiller University, Jena, Germany.

1. 4-Thio-6-methyl-2-(p-methoxyphenyl)-5-acetylpyrimidine **1**:

Was prepared according to the reported procedure[7].

2. Carboxymethylmercaptopyrimidine derivative **2**:

A mixture of compound **1** (0.01 mole) was dissolved in sodium carbonate solution (0.02 mole) on hot and was added to (0.01 mole) of chloroacetic acid, which dissolved also in sodium carbonate solution (0.01 mole). The reaction mixture was heated at 60ºC for 20 minutes. The solid product obtained upon the addition of HCl (10 ml, 20%), was collected and crystallized from benzene to give colorless crystals **2** (**Table 1**).

3. Thienopyrimidine derivative **5**:

A mixture of acid chloride **3** (0.01 mole) [was prepared by refluxing of **2** (0.01 mole) and thionyl chloride (0.01 mole) on water bath for 1 hour] and 3-carboxamide derivative **4** (0.01 mole) was heated under reflux in dry dioxane (20 ml) for four hours. The solid obtained upon evaporation and dilution with water (10 ml) was filtered and crystallized from ethanol to give brown crystals **5** (**Table 1**).

4. Thienopyrimidinylthienopyrimidine **6**:

A mixture of thienopyrimidine derivative **5** (0.01 mole) and TEA (3 drops) in absolute ethanol was refluxed for four hours. The solid obtained upon evaporation and dilution with water (10 ml) was filtered and crystallized from methanol to give brown crystals **6** (**Table 1**).

5. N-(*o*-aminophenyl)thienopyrimidinecarboxamide **7**:

An equimolar amounts of acid chloride **3** (.01 mole) and *o*-phenylenediamine (0.01 mole) in dry dioxane (20 ml) was stirred at room temperature for two hours. The solid obtained upon dilution with water (20 ml) was collected and crystallized from acetic acid to give yellow crystals **7** (**Table 1**).

6. Benzimidazolthienopyrimidine **8**:

A solution of thienopyrimidine derivative **7** (0.01 mole) in dry dioxane (20 ml) was refluxed for six hours. The solid obtained upon concentration and dilution with water (20 ml) was collected and crystallized from acetic acid to give brown crystals **8** (**Table 1**).

7. N-(*o*-hydroxyphenyl)thienopyrimidinecarboxamide derivative **9**:

An equimolar amounts of acid chloride **3** (0.01 mole) and *o*-aminophenol (0.01 mole) in dry dioxane (20 ml) was stirred at room temperature for two hours. The solid obtained upon dilution with water (20 ml) was collected and crystallized from acetic acid to give yellowish crystals **9** (**Table 1**).

8. Benzoxazolylthienopyrimidine **10**:

Refluxing thienopyrimidine derivative **9** in acetic anhydride in water path for two hours. The solid obtained upon concentration and pouring on ice was collected by filtration and crystallized from acetic acid to give brown crystals **10** (**Table 1**).

9. 4-[O-carboxyphenylcarbamylmethylthio]-6-methyl-2-(p-methoxyphenyl)-5-acetylpyrimidine **12**:

A mixture of N-(*o*-carboxyphenyl)chloroacetamide **11** (0.01 mole) and 4-thio-6-methyl-2-(*p*-methoxyphenyl)-5-acetylpyrimidine **1** (0.01 mole) in (30 ml) dimethylformamide in presence of TMA (4 drops) was heated under reflux for five hours, the solid obtained upon concentration and crystallized from benzene to give yellow crystals **12** (**Table 1**).

10. 2-Thieno[2,3-d]pyrimidinyl-4H-3,1-benzoxazine-4-one **13**:

A mixture of compound **12** (0.01 mole), acetic anhydride (10 ml) and fused sodium acetate (5g) was refluxed for two hours, a solid product was obtained after cooling and was crystallized from dry benzene giving yellow needles **13** (**Table 1**).

11. 2-Thieno[2,3-d]pyrimidinyl-3-aryl-4(3H)quinazolinone **14a,b**:

A solution of compound **13** (0.01 mole) and primary aromatic amines namely aniline and m-chloroaniline (0.01 mole) in boiling dry dioxane (20 ml) was heated under reflux for five hours, the products **14a,b** that seprated on cooling were crystallized from benzene (**Table 1**).

12. 2-Thieno[2,3-d]pyrimidinyl-3-amino-4(3H)quinazolinone **14c**:

A solution of benzoxazine **13** (0.01 mole) and hydrazine hydrate (0.01 mole) in dry dioxane (60 ml) was heated under reflux for five hours, the solid separated upon cooling were crystalized from benzene to give compound **14c** (**Table 1**).

TABLE I

Physical data of compounds (5-18).

Compound	Colour	m.p. (ºC) (Yield %)	Formula (Molecular mass)	Micro analyses Calcd. / Found (%)		
				C	H	N
2	Colourless	166 (70)	$C_{16}H_{16}N_2O_4S$ 332.08	57.82 57.70	4.86 4.80	8.43 8.40
5	Brown	150 (60)	$C_{25}H_{24}N_4O_3S_2$ 492.12	60.96 60.90	4.91 4.80	11.38 11.30
6	Brown	210 (56)	$C_{25}H_{22}N_4O_2S_2$ 474.11	63.28 63.20	4.68 4.60	11.81 11.70
7	Yellow	200 (65)	$C_{22}H_{20}N_4O_2S$ 404.13	65.33 65.00	4.99 4.90	13.86 13.80
8	Brown	250 (58)	$C_{22}H_{18}N_4OS$ 386.12	68.37 68.30	4.70 4.60	14.51 14.40
9	Yellowish	246 (45)	$C_{22}H_{19}N_3O_3S$ 405.11	65.17 65.10	4.73 4.60	10.37 14.40
10	Brown	230 (40)	$C_{22}H_{17}N_3O_2S$ 387.10	68.20 68.10	4.43 4.30	10.85 10.80
12	Yellow	222 (70)	$C_{23}H_{21}N_3O_4S$ 451.50	61.19 61.18	4.69 4.60	9.31 9.30
13	Yellow	222 (68)	$C_{23}H_{17}N_3O_3S$ 415.12	66.49 66.30	4.13 4.11	10.12 10.03
14a	Yellow	270 (80)	$C_{29}H_{22}N_4O_2S$ 478.14	70.27 70.10	4.64 4.50	11.71 11.60
14b	Yellow	280 (79)	$C_{29}H_{21}N_4O_2SCl$ 524.10	66.40 66.30	4.03 4.00	10.69 10.60
14c	Yellow	290 (73)	$C_{23}H_{19}N_5O_2S$ 429.12	64.32 64.20	4.46 4.40	16.32 16.30
16	Yellow	230 (59)	$C_{23}H_{18}N_4O_2S$ 414.11	66.65 66.50	4.38 4.30	13.53 13.50
18	Yellow	286 (80)	$C_{24}H_{18}N_6O_2S$ 454.12	63.42 63.30	3.99 3.90	18.50 18.40

TABLE II

Compound	IR (Cm^{-1}) Selected band
2	1680, 1700 (C=O) and 3500 (OH).
7	1656 (C=O) of amide and 3288 (NH, NH_2).
9	1606 (C=O) of amide and 3404 (NH, OH).
10	1604 (C=N).
12	1683, 1690, 1720 (C=O) and 3424 (NH).
14a,b	1596 (C=N) and 1754 (C=O).
14c	1754 (C=O) and 3254 (NH).
16	1602 (C=N), 1682 (C=O) and 3156 (NH).
18	1598 (C=N), 1760 (C=O) and 3440 (NH).

TABLE III

Compound	^{1}H NMR (δ DMSO – d_6), δppm
6	1.90 (s, 3H, CH_3), 2.60 (s, 3H, CH_3) 3.59 (s, 3H, OCH_3), 2.61-2.90 (m, 8H, CH_2) cyclohexane proton 6.90-8.38 (m, 4H, Ar H's) and 12.94 (s, 1H, NH).
8	2.55 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.91-8.41 (m, 8H, Ar H's) and 12.2 (s, 1H, NH).
9	2.48 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.93-8.50 (m, 8H, Ar H's), 9.72 (s, 1H, NH) and 9.93 (s, 1H, OH).
14a	2.40 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3) and 6.90-8.30 (m, 13H, Ar H's).
14c	2.40 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3) and 7.00-8.40 (m, 10H, Ar H's + NH_2 protons).
18	2.90 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3) and 7.00-8.50 (m, 9H, Ar H's + NH proton).

13. 2-Thieno[2,3-d]pyrimidinyl-4(3H)quinazolinone **16**:

A mixture of benzoxazine **13** (0.01 mole) and formamide (0.1 mole) was heated under reflux for five hours. The product obtained upon concentration and cooling was crystallized from benzene to give yellow needles **16** (**Table 1**).

14. 2-Thieno[2,3-d]pyrimidinyltriazoloquinazoline **18**:

A mixture of benzoxazine **13** (0.01 mole) and semicarbazide (0.01 mole) in dry dioxane (20 ml) was heated under reflux for five hours. The solid obtained upon concentration and cooling was collected and crystallized from benzene to give yellow crystals **18** (**Table 1**).

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