

## Synthesis of Some Heterocyclic Compounds derived from 2-mercapto pyrimidine

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### Abstract:

In this work 2-hydrazino pyrimidine (**1**) was prepared from 2-mercapto pyrimidine with hydrazine hydrate.

Treatment of (**1**) with active methylene compounds gave 2-(3,5-dimethyl -1 H – Pyrazole-1-yl) pyrimidine , whereas the reaction of (**1**) with carboxylic anhydride namely maleic anhydride or 1,2,3,6-tetra hydro phthalic anhydride yielded 1-Pyrimidine-2-yl-1,2-dihydro pyridazine-3,6-dione (**3**) and 2 – Pyrimidin -2-yl -2,3,4 a ,5,8 a – hexahydro phthalazine 1,4 – dione (**4**) .

Reaction of (**1**) with phenyl isothiocyanate and ethyl chloro acetate afforded 3-Phenyl-1,3-thiazolidine-2,4-dione-2( pyrimidine -2- yl) hydrazone (**6**)

Azomethine (**7-10**) were prepared through condensation of (**1**) with aromatic aldehydes or ketones, then compounds (**7-9**) are converted into a number of tetrazole derivatives (**11-13**).

Treatment of (**1**) with acetic acid afforded the derivative (**14**) .

The reaction of 2-mercapto pyrimidine with ethyl chloro acetate afforded (**15**), whereas the reaction of (**15**) with thiosemicarbazide and 4% sodium hydroxide leads to ring closure giving 1,2,4 triazole derivative (**17**).

Moreover the reaction of 2-mercapto pyrimidine with chloro acetic acid gave (**18**) followed by refluxing (**18**) with o- amino aniline to give the benzimidazole derivative (**19**). The structure of these compounds were characterized by FR-IR, UV spectra and some of them were characterized by element analysis.

**Key words:** 2-mercapto pyrimidine, pyrazol, 1,2,4-triazole, Pyridazine.

### Introduction:

Pyrazole derivatives have attracted particular interests during the last twenty five years due to the use of such ring system as the core structure in many drug substances , covering wide range of pharmacological applications [1,2]

Synthetic pyridazinone derivatives as important scaffolds in drug discovery, with many of their analog being used in the treatment of various human pathological states.[3] 4-Thiazolidinone derivatives play a vital role owing to their wide range of biological activity and industrial importance as stabilizers for polymeric materials [4,5].

In recent years, derivatives of Schiff bases ,1,2,4-triazole and tetrazole have been found to exhibit some biological and pharmaceutical properties [6], antibacterial[7] antihistaminic[8], antifungial [9] anti-inflammatory [10].

Benzimidazole and its derivatives have attracted researcher's interest in the fields of bioorganic and medical chemistry to their significant antifungal, antibacterial and insecticidal properties [11].

We now report on the synthesis of compounds derived from 2-mercapto pyrimidine containing pyrazole, Pyridazine thiazolidinone, tetrazole,

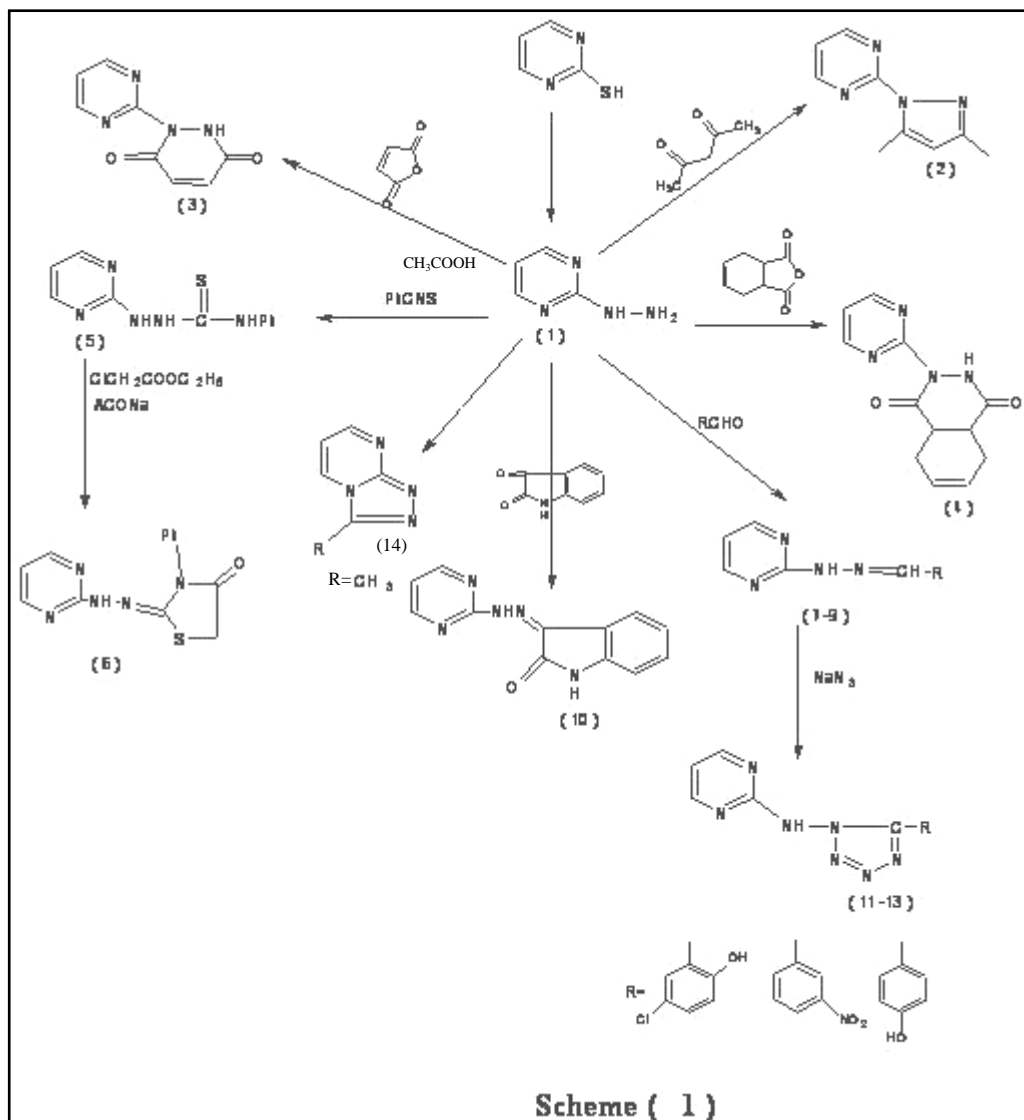
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triazole and benzimidazole moieties, with the purpose of investigating in the future their possible antibacterial and antifungal activities.

## Result and Discussion:

The reaction sequence for titled compounds is outlined in Schemes 1, 2.



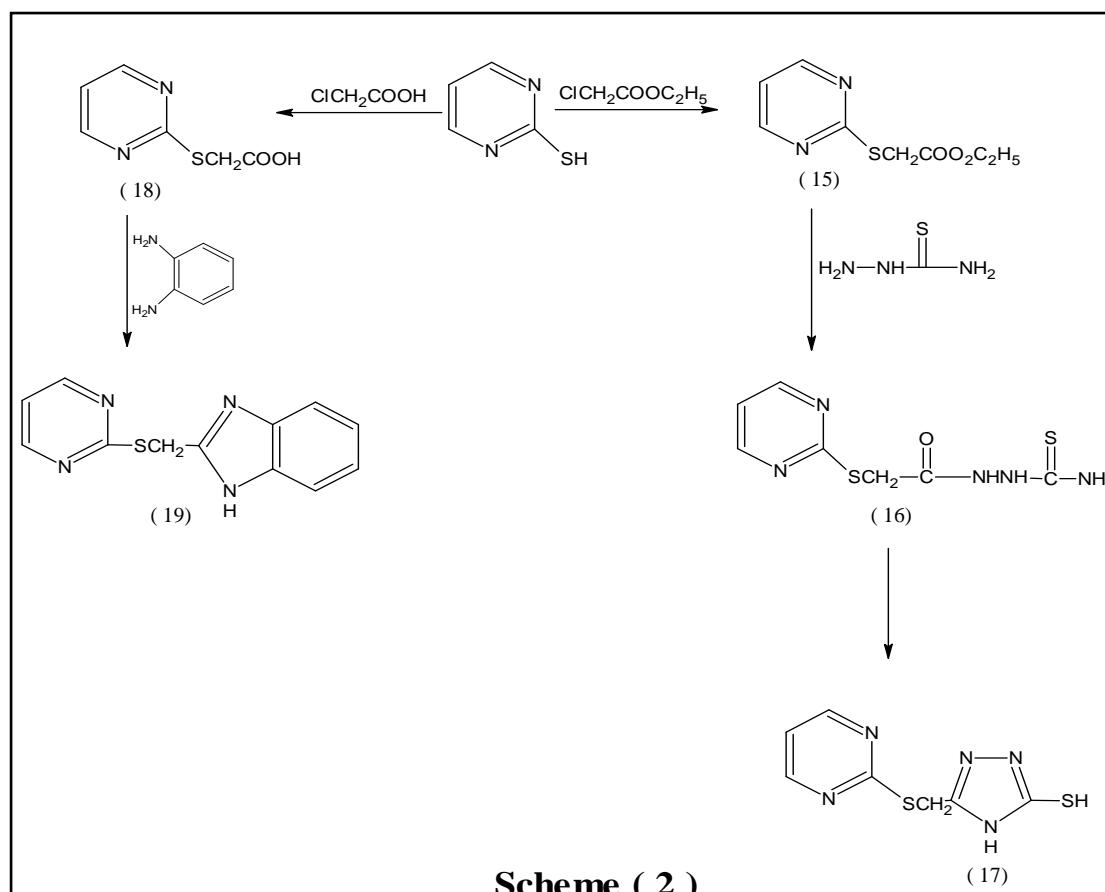
Scheme ( 1 )

(1) which was prepared by the reaction of 2-mercapto pyrimidine with hydrazine hydrate. The starting material for the synthesis of targeted compounds is 2-hydrazino pyrimidine.

Treatment of (1) with active methylene compound such as acetyl

acetone produced pyrazolo derivative (2).

The structure of (2) was confirmed by their *FTIR* and *UV* spectra through the appearance of the band at  $1371\text{cm}^{-1}$  for  $\text{CH}_3$  bending vibration and disappearance of the  $\text{NH}_2$  and  $\text{NH}$  stretching bands in (2).



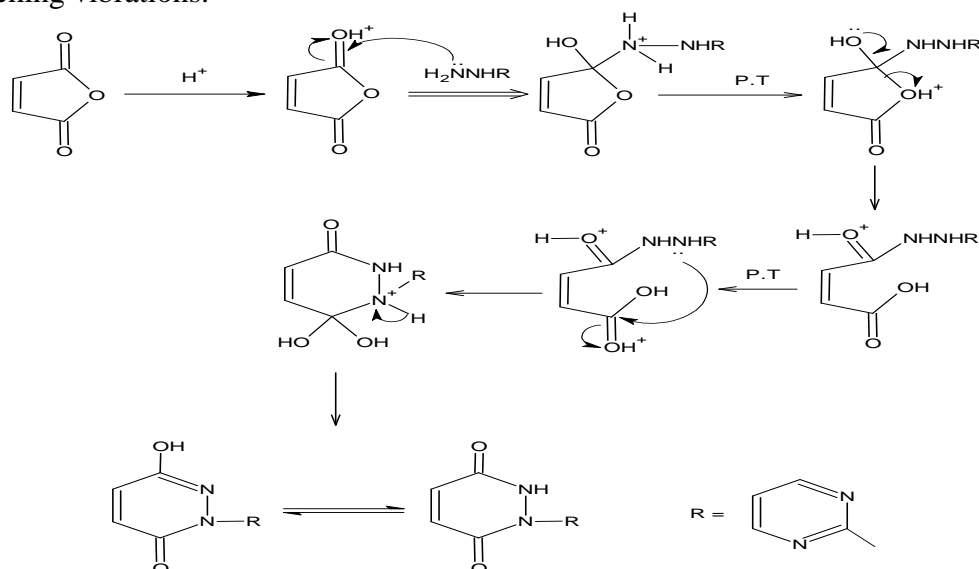
Treatment of (1) with carboxylic anhydrides, e.g. maleic anhydride and 1,2,3,6-tetrahydrophthalic anhydride gave 1-(Pyrimidine-2-yl)-1,2-dihydro pyridazin-3,6-dione (3) and compound (4).

*FTIR* spectrum of (3) shows broad bands at  $3450\text{ cm}^{-1}$  and  $3221\text{ cm}^{-1}$  which were assignable to (NH) stretching vibrations.

The stretching vibration band at  $1716\text{ cm}^{-1}$  was due to  $\nu(\text{C}=\text{O})$  moiety of pyridazine ring while the  $(\text{C}=\text{O})$  stretching of amide  $1624\text{ cm}^{-1}$ .

We can say that compounds (3) or (4) can exist in two tautomeric forms, keto and enol forms.

The mechanism of reaction is shown in scheme (3).



Reaction between (1) and phenyl isothiocyanate afforded the corresponding thiosemicarbazide 5 in moderate yield.

The *FTIR* spectra of (5) display (C=S) stretching band at  $1255\text{cm}^{-1}$  and (NH) stretching band at  $3227\text{cm}^{-1}$ .

Refluxing of compound (5) with ethylchloroacetate and anhydrous sodium acetate in absolute ethanol for six hours afforded 4- thioazolidone (6). The structure of (6) was confirmed by the presence of (C=O) stretching band at  $1720\text{cm}^{-1}$  and (C=N) stretching band at  $1643\text{cm}^{-1}$ .

Condensation of (1) with aryl aldehydes or Isatin in absolute ethanol gave the Schiff's bases (7-10).

The formation of these Schiff bases was indicated by the presence in their *FTIR* spectra of azomethine (C=N) stretching band at  $1600\text{-}1640\text{cm}^{-1}$ , combined with the disappearance of  $\text{NH}_2$  stretching band.

Moreover, treatment of Schiff's bases (7-9) with ( $\text{NaN}_3$ ) produced tetrazole derivatives(10-13).

Structures of these compound, were confirmed by the disappearance of band at  $(1600\text{-}1640)\text{cm}^{-1}$ , attributed to (C=N) (imine group) stretching frequency which was a good evidence for the success of this step of reaction. Beside this, *FTIR* spectra of these compounds were devoid of a strong band at  $(2160\text{-}2120)\text{cm}^{-1}$  attributed to stretching frequency of azide group.

A band at the range  $(1136\text{-}1087)\text{cm}^{-1}$  was due to tetrazole ring[12]. Treatment of (1) with acetic acid gave 5- methyl -1,2,4-triazolo-[4,3-a]-Pyrimidine (14).

The *FTIR* spectra of (14) showed a band at  $1380\text{cm}^{-1}$  for the (C-H) in ( $\text{CH}_3$ ), in addition to the band at  $1635\text{cm}^{-1}$  for (C=N) stretch.

On the other hand the reaction of starting material 2-mercapto pyrimidine with ethylchloroacetate afforded (15), which displayed (C=O)

stretching band at  $1737\text{cm}^{-1}$ .

Treatment of (15) with powdered thiosemicarbazide in dry benzene afforded the acylthiosemicarbazide (16), Which upon ring closure with 4% NaOH gave 5-(pyrimidine -2- yl thio methyl)-4H-1,2,4-triazole -3- thiol (17)[13], which exists in a tautomeric thiol -thione equilibrium as indicated by the C=S stretching band at  $1180\text{cm}^{-1}$  and S-H stretch at  $2550\text{cm}^{-1}$  [14].

In order to synthesize pyrimidine -2-yl-mercapto-acetic acid (18), the starting material 2-mercapto pyrimidine was react with mono-Chloro acetic acid. Condensation of compound (18) with o-phenylene diamine yielded the benzimidazole derivative (19). Structure of compound (19) was confirmed by *FTIR* spectra data which showed the disappearance of bands at  $3400\text{cm}^{-1}$  and  $1718\text{cm}^{-1}$  attributed to (OH) and (C=O) of carboxylic acid in compound (18). Elemental analysis proved the structural formula for some compounds as well as the purity of each compounds.

## Material and Methods:

### General

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra discs (KBr) were recorded with a Shimadzu *FTIR*-8400, UV spectra were recorded on a Shimadzu 160A UV/VIS spectrophotometer using absolute ethanol as solvent. Element analysis were done on EURO EA instrument in Al - Mustansiriya University. Starting chemical compounds were obtained from Fluka or BDH.

### Preparation of 2-hydrazino pyrimidine (1):

A mixture of 2-mercapto pyrimidine (0.01 mole, 1.12g) and hydrazine hydrate (10 ml) was refluxed for

3hours, ethanol (15ml) was added and refluxed for 4 hours. The separated precipitate was filtered and washed with cold water and recrystallized from ethanol.

#### **Preparation of 2-(3,5-dimethyl-1H-Pyrazol-1-yl)pyrimidine (2):**

To a solution of Compound (1)(0.002 mole,0.22g) in absolute ethanol (20 ml) was added acetyl acetone (0.002 mole,0.2ml).The reaction mixture was refluxed for 6 hours .After concentration and cooling, the solid product that formed was filtered and recrystallized from ethanol. Compound (2), Calc. For  $C_9H_{10}N_4$ (%): C,62.20;H,5.75;N,32.16; found% : C: 62.38, H: 5.58; N: 31.94.

#### **General procedure for preparation of 1-pyrimidine -2- yl 1,2-dihydropyridazine-3,6-dione (3) and 2-pyrimidine -2-yl-2,3,4a,5,8, 8a-hexa hydro phthalazine-1,4-dione(4)[15]**

Maleic anhydride or 1,2,3,6-tetrahydro phthalic anhydride ( 0.01 mole) in (30ml)acetic acid was added to hydrazide (1) (0.01 mole,1.1g) and the reaction was refluxed for (7 hours) . Then the mixture was poured on crushed ice,the formed solid product was filtered off and recrystallized from pet.ether (40-60) $^{\circ}C$  .

#### **Preparation of N- Phenyl -2-Pyrimidine-2-yl-hydrazine carbothio-amide (5).**

A mixture of Compound (1) (0.01 mole,1.1g) and phenyl isothiocyanate (0.011 mole,1.31ml),in absolute ethanol (20ml) was refluxed for 3hours and cooled . The solid product was filtered and recrystallized from ethanol . Compound (5), Calculated For  $C_{11}H_{11}N_5S$ (%): C,53.87; H,4.48; N,28.57; S,13.06; Found(%) :C,53.99; H,4.61; N,28.60; S,12.80.

#### **Preparation of 3- phenyl -1,3-thiazolidine -2,4-dione-2-(Pyrimidine-2-yl-hydrazone) (6)**

Ethyl chloro acetate (0.01 mole,0.9g) was added dropwise to a stirred solution of compound (5) (0.01 mole,2.4g) and anhydrous sodium acetate (0.01mole) in (20ml) absolute ethanol. The reaction mixture was refluxed for 6hours. The solid product was filtered and recrystallized from ethanol .

#### **Preparation of Compounds (7-10)**

A mixture of compound (1) (0.002mole,0.22g) and the corresponding aryl aldehyde or Isatin (0.002 mole) in absolute ethanol (20 ml) was refluxed for (3 hours) and cooled . The solid product was filtered and recrystallized from ethanol .

#### **Preparation of 2-[5-Substituted-tetrazol-1-yl]-Pyrimidine( 11-13 )**

A mixture of (0.002mole) of appropriate Schiff base (7-9),dry acetone (15ml) and sodium azide (0.002 mole,0.13g) was heated on a water bath , the temperature of the water bath was controlled between (50-55 $^{\circ}C$ ).

The end of the reaction was checked by TLC which showed the disappearance of the starting material .

#### **Preparation of 5- methyl-1,2,4-triazole[4,3-a]-pyrimidine (14).**

The solution of compound (1) (0.003 mole,0.33g) in glyacial acetic acid(10ml)was heated under vacuum as much as possible and the mixture was poured onto ice-cold water .The solid was filtered ,washed with water and recrystallized from ethyl acetate. Compound (14) ,Calc. for  $C_6H_6N_4$  (%):C,53.73;H,4.47;N, 41. 79; found (%):C,53.85; H,4.10; N,42.05 .

**Preparation of Ethyl –(pyrimidine-2-thio)acetate (15)**

Ethyl chloro acetate (0.01mole,0.95g) was added dropwise to a stirred solution of 2- mercaptopyrimidine (0.01mole,1.12g) and KOH (0.56gm, 0.01 mole) in (20ml) absolute ethanol. The reaction was mixture refluxed for (5 hours).The solid was filtered, washed with water and recrystallized from chloroform. Compound (15): Calc. for  $C_8H_{10}N_2O_2S$  (%) :C,48.48;H,5.05; N,14.14;S,16.16; found (%) :C,48.30;H,4.90;N, 13.90; S,16.00.

**Preparation of 2- [(pyrimidine-2-yl-thio)acetyl]hydrazinecarbothio amide (16)**

To solution of compound (16) (0.01 mole,1.71g) in absolute ethanol (20 ml) was added thiosemicarbazide (0.01mole,0.92g). The mixture was refluxed for 4hour and after cooling the precipitate was filtered and recrystallized from ethanol – water .

**Preparation of 5-(pyrimidine-2-yl-thiomethyl)-4H-1,2,4-triazole-3-thio (17)**

A stirred mixture of compound (17)(0.03mole,0.633g) and aqueous

sodium hydroxide (4%,10ml) was refluxed for (3 hours). The mixture was acidified with dil. HCl and the precipitate was collected crystallized from ethanol.

**Preparation of pyrimidine-2-yl-mercapto acetic acid (18)**

To (0.01 mole,1.12g) of 2-mercapto pyrimidine in (20 ml) of ethanol (0.01 mole) of KOH was added followed by (0.01 mole,0.95g) of monochloroacetic acid. The reaction mixture was heated under reflux for (8 hours). The hot solution was evaporated under reduced pressure. The solid was filtered washed with cold distilled water. and recrystallized from ethanol

**Preparation of 2-(1H-benzimidazol-2yl-thiomethyl)pyrimidine (19)**

Compound (18) (0.01 mole,1.7g) was refluxed for 12 hours with o-phenylene diamine (0.01 mole,1.08g) in 4N hydrochloric acid (20ml). the reaction mixture was cooled and then neturalized with ammonia to precipitate benzimidazole. The crude product was recrystallized from ethanol .

All physical constant for these compounds were reported in table-1

**Table.1. physical constants and spectroscopic data for compounds.**

Com. No.	Formula	MP. °C	Yield %	UV, $\lambda_{\max}$ (EtOH)	Infrared data ( $\nu, \text{cm}^{-1}$ ) (KBr disc)
1	$\text{C}_4\text{H}_6\text{N}_4$	226-228	75	250, 339	3290, 3185(N-H) , 3084(C-H <sub>ar</sub> ), 1560,(C=C) ,1630(C=N);
2	$\text{C}_9\text{H}_{10}\text{N}_4$	110-112	60	285 320 389	3030(C-H <sub>ar</sub> ),2926(C-H) , 1614(C=N), 1568(C=C)
3	$\text{C}_8\text{H}_6\text{N}_4\text{O}_2$	188-190	50	204 245	3450(OH), 3221(NH),2939 (C-H), 1716(C=O)1624(C=O <sub>amid</sub> )
4	$\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}_2$	220-222	65	240 380	3240(N-H) , 2928(C-H <sub>al</sub> ), 1697 (C=O),1654(C=O <sub>amid</sub> )
5	$\text{C}_{11}\text{H}_{11}\text{N}_5\text{S}$	200-202	72	204 262 367	3227, 3186 (N-H), 3030(C-H <sub>ar</sub> ),1255 (C=S),1629(C=N) ,1554(C= C)
6	$\text{C}_{13}\text{H}_{12}\text{N}_5\text{OS}$	226-228	65	202 265 315	3458(N-H),3084(C-H <sub>ar</sub> ),1720 (C=O <sub>amide</sub> ),1643(C=N),676(C-S-C)
7	$\text{C}_{11}\text{H}_9\text{N}_4\text{OCl}$	254-256	82	204 260 290	3309(OH),3105(NH) ,3020 (C- H <sub>ar</sub> ),1631(C=N <sub>exocycl</sub> ), 1572(C=N <sub>indocycl</sub> ),820(C-Cl)
8	$\text{C}_{11}\text{H}_9\text{N}_5\text{O}_2$	248-250	83	206 270 288	3281(NH),1640(C=N <sub>exo</sub> ),1581 (C=N <sub>indo</sub> ),1336(NO <sub>2 sym</sub> ),1510(NO <sub>2 asym</sub> ),
9	$\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}$	230-232	80	208 287 302	3320(OH),3211(NH),3090(C-H <sub>ar</sub> ), 1646(C=N <sub>exo</sub> ),1590(C=N <sub>indo</sub> )
10	$\text{C}_{12}\text{H}_9\text{N}_5\text{O}$	202-204	79	210 260 300	3319,3211(NH),3100(C-H <sub>ar</sub> ), 1685(C=O <sub>amide</sub> ),1645(C=N)
11	$\text{C}_{11}\text{H}_8\text{N}_7\text{OCl}$	200-202	65	204 249 396	3300-3000(OH),3281(NH),1610 (C=N)1095,1136(tetrazol),814 (C-Cl)
12	$\text{C}_{11}\text{H}_8\text{N}_8\text{O}_2$	234-236	60	204 240 310	3390(NH),1626(C=N),1342(NO <sub>2sym</sub> ), 1519 (NO <sub>2asym</sub> ),1012,1105(tetrazol)
13	$\text{C}_{11}\text{H}_9\text{N}_7\text{O}$	228-230	58	202 255	3269(OH),3260(NH),1635(C=N) 1157,1087(tetrazol)
14	$\text{C}_6\text{H}_6\text{N}_4$	229-231	78	204 260	3070(C-H <sub>ar</sub> ),2988(C-H <sub>al</sub> ),1635(C=N), 1590(C=C),1380(CH <sub>3 bend</sub> .)
15	$\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2\text{S}$	196-198	73	204 254 312	3098(C-H <sub>ar</sub> ),2978(C-H <sub>al</sub> ),1737(C=O <sub>ester</sub> ) 1250(C-O),640(C-S)
16	$\text{C}_7\text{H}_9\text{N}_5\text{OS}$	210-212	67	230 375	3379,3263(NH <sub>2</sub> ),3153(NH),2997(C-H <sub>al</sub> ) 1660(C=O),1300,1269,1109(NHC=S)
17	$\text{C}_7\text{H}_7\text{N}_5\text{S}_2$	211-213	60	202 250 360	3160(NH),2550(SH),1640(C=N) 1180(C=S)
18	$\text{C}_6\text{H}_6\text{N}_2\text{O}_2\text{S}$	250-252	72	220 380	3400-2500(OH),3030(C-H <sub>ar</sub> ),2930 (C- H <sub>al</sub> )1718(C=O),1565(C=N)
19	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{S}$	240-242	67	204 387	3180(NH),3064(C-H <sub>ar</sub> ),2982(C-H), 1640(C=N),720(C-S)

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## تحضير بعض المركبات الحلقية الغير المتجانسة المشتقة من 2- مركبتو بريميدين

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## الخلاصة

في هذا العمل حضر 2-هايدرازوبريميدين (1) من 2-مركبتو بريميدين مع هايدرازين اللامائي. وبمعاملة (1) مع المركبات الحاوية على مثلين فعالة اعطت 2-(3و5-ثنائي -1H-بايروزول-1-يل) بريميدين، بينما تفاعل (1) مع انهيدريدات الحوامض الكربوكسيلية مثل انهيدريد المالك او انهيدريد 6,3,2,1-تتراهيدرو الفثاليك اعطت 1-بريميدين-2-يل-1,2-ثنائي بيردايازين-3و6 ثنائي اون (3) و 2-بريميدين -2-يل - 4,3,2-a, 5,8-سداسي هايدروفثالزين - 4,1 - ثنائي اون (4) . تفاعل (1) مع فنييل ايزوثايوسيانيت و اثيل كلورواستات تكون 3-فنييل - 1,3 - ثايوزوليدين - 4,2-ثنائي اون -2 (بريميدين -2-يل - هايدرزون ) (6) .

مركبات ازوميثين (7-10) حضرت من خلال تكاثف (1) مع الالديهيدات الاروماتية او الكيتون ، ثم المركبات (7-9) تم تحويلها الى عدد من مشتقات التترازول (11-13) . معاملة (1) مع حامض الخليك اعطى المشتق (14). وتفاعل 2-مركبتوبريميدين مع اثيل كلورواستات اعطى (15) وتفاعل (15) مع ثايوسيمكاربازيد في محيط قاعدي ادى الى الغلق الحلقي الذي اعطى المشتق 4,2,1-ترايزول (17). تفاعل 2-مركبتوبريميدين مع حامض كلورو اسيتيك اعطى (18) يتبعه تصعيد (18) مع اورثو- امينواتلين ليعطي المشتق بنزايميدازول (19) تم تشخيص المركبات المحضرة بواسطة الاشعة تحت الحمراء المعززة بتحويلات فورير والاشعة فوق البنفسجية وكذلك بعض منها تم تشخيصها باستخدام التحليل الدقيق للعناصر.