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SYNTHESIS AND BIOLOGICAL EFFECT OF SOME THIENO[2,3-D] PYRIMIDINE-4-(3H) ONE

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Abstract

Interaction of thiophene enamino ester **1a,b** with the acid chloride of p-tolyl sulphonamido-N-acetic acid derivatives 2a-c afforded the corresponding amide derivatives respectively **3a-f**. Hydrazinolysis of **3a-f** with hydrazine hydrate yielded **4a-f**. Diazotization of **1a** then coupling with different amines gave **6a,b**. compounds **7a,b** was afforded when diazonium chloride of p-toludin or enamino thiophene 3-carboxylate **(5)** was reacted with compound **1a**. Air oxidation of **6a** yielded **8**. Coupling was carried out with different amines compounds where **5** yielded **9a,b**. According to Gewald method **11a-b** was prepared from reaction of **10a,b** with malononitrile, From **11a,b** we can prepare compounds **13, 14a-c, 15a-c 16a,b, 17a,b, 18, 19 and 20**.

The structure of these compounds was confirmed by infrared, mass, H-NMR spectra the biological activity of some compounds were discussed and found to be active.

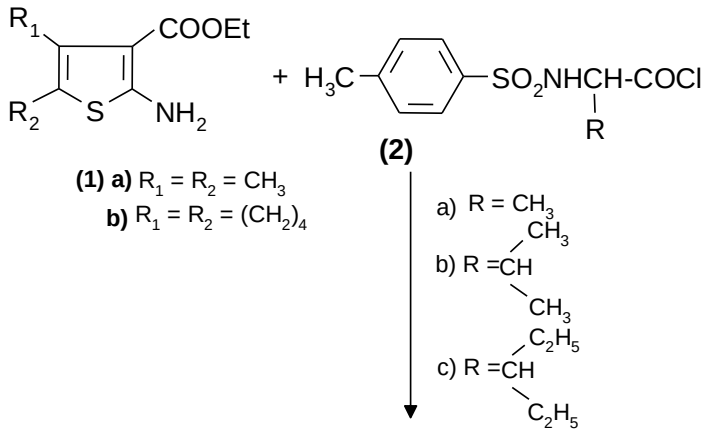
Introduction

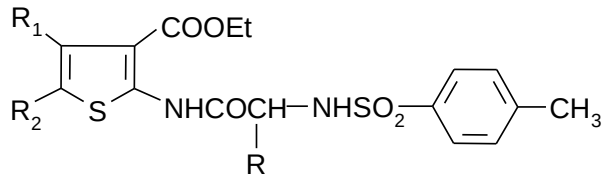
Many thienopyrimidine derivatives have been found to posses a wide span of medical activities including antihistaminic[(1)], antitumour[(2)], antibriltatory[(3)] and hypoglycemic[(4)]. Furthermore, diverse biological properties had been shown to be associated with numerous thienopyrimidine and thiazolothienopyrimidine comprising hypnolic[(5)], antiviral[(6,7)] and plant bactericidal affects[(8).]

The aromatic rings and a side chain with a basic sulphonamide are the essential pharmacophoric activity of several thienopyrimidine derivatives.

Results and Discussion

The thiophene amide derivatives **(3a-c)** were obtained from the reaction of thiophene enamino ester[(9,10)] with the acid chloride derivatives of *p*-tolylsulphonamide-N-acetic acid **(2a-c).**



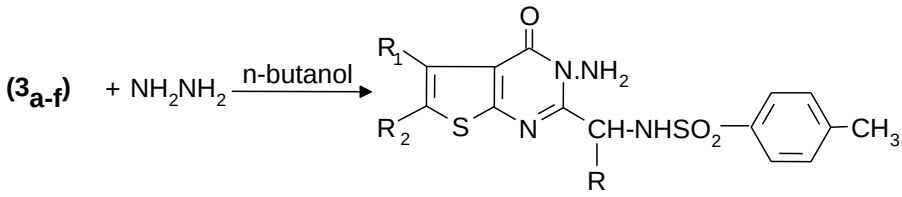


(3_{a-f})

a) $R_1 = R_2 = R_3 = CH_3$,
b) $R_1 = R_2 = CH_3$, R = $CH(CH_3)_2$
c) $R_1 = R_2 = CH_3$, R = $CH(CH_3)C_2H_5$
d) $R_1 = R_2 = (CH_2)_4$, R = CH_3
e) $R_1 = R_2 = (CH_2)_4$, R = $CH(CH_3)_2$
f) $R_1 = R_2 = (CH_2)_4$, R = $CH(CH_3)C_2H_5$

Compounds **(3a-f)** were confirmed by elemental analysis and spectroscopic evidences. Infrared spectra revealed absorption bands for NH and C=O group as shown in (Table 1).

The reaction of the amide derivatives **(3a-f)** with hydrazine hydrate in *n*-butanol affected cyclization to afford the desired derivatives of N-amino theino [2,3-d] pyrymidin-4- (3H)-one **(4_{a-f})**.



(4_{a-f})

a) $R_1 = R_2 = R = CH_3$

b) $R_1 = R_2 = CH_3$, $R = CH(CH_3)_2$

c) $R_1 = R_2 = CH_3$, $R = CH(CH_3)C_2H_5$

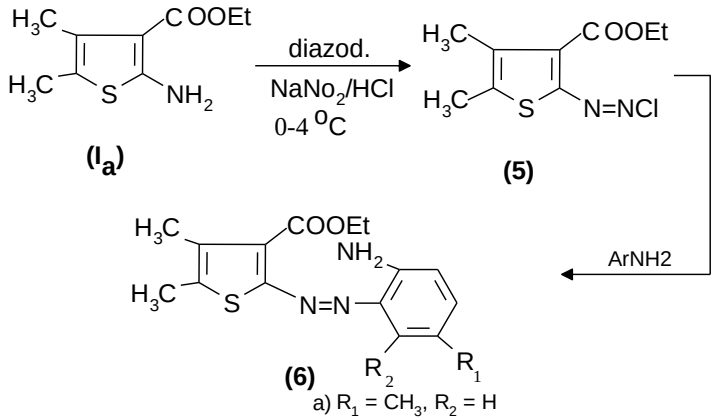
d) $R_1 = R_2 = (CH_2)_4$, $R = CH_3$

e) $R_1 = R_2 = (CH_2)_4$, $R = CH(CH_3)_2$

f) $R_1 = R_2 = (CH_2)_4$, $R = CH(CH_3)C_2H_5$

Structure **(4a-f)** were supported by elemental analysis (Table 3) and spectral data (Table 2).

Azo thiophene derivatives have been found to posses good medicinal and biological activities[11,12]. So compound **(1a)** enamino thiophene ester was diazotized **(5)** and coupled with different aromatic amines namely *p*-toluidine or β-naphthylamine in presence of acetic acid to give o- aminoarylazo derivatives **(6a,b)**



(I_a) **(5)**

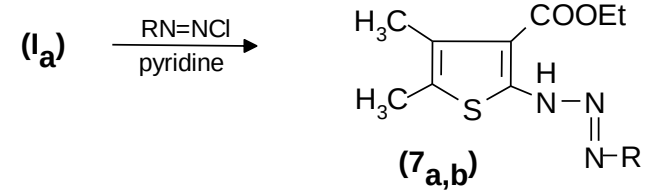
(6)

a) $R_1 = CH_3$, $R_2 = H$

b) $R_1 = R_2$=benzo

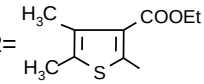
Structure of **(6a,b)** were supported by spectroscopic data and elemental analysis (Table 3).

When the diazonium chlorides of *p*-toluidine or enamino thiophene-3-ethylester **(5)** were reacted with enamino thiophene ester **(1a)** in presence of pyridine, it afforded N-arylazo thiophene derivatives **(7a,b).**



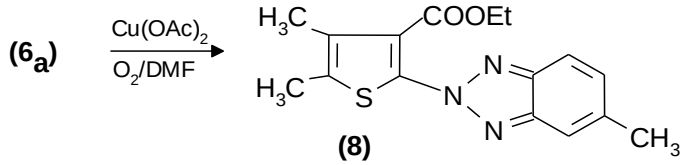
(7a,b)

a) R = $-C_6H_4CH_3$ -*p*

b) R= 

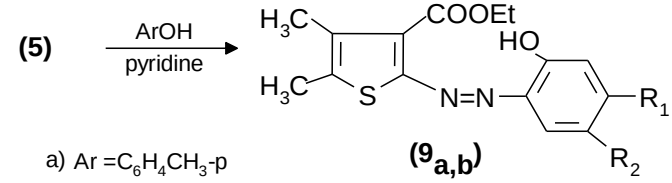
The structure of **(7a,b)** were established according to spectroscopic and elemental data (Table 3).

The o-aminoaryl **(6a)** derivative on subsequent air oxidation in presence of a cupric salt yielded 2-N-(4,5 dimethyl thiophen-2-yl) benzo-1,2,3-triazol derivative **(8)**[13].



(8)

On the other hand, when the coupling was carried out between diazonium salt **(5)** and different phenols (*p*-cresol and resorcinol) in presence of pyridine the dye derivatives 2-(1-hydroxy-4-methylphenyl or 1,3-dihydroxyphenyl azo) -4,5-dimethyl thiophene-3-carboxylate ester **(9a,b)** were obtained.



a) Ar =$C_6H_4CH_3$-p

b) Ar = C_6H_4OH m-

(9a,b)

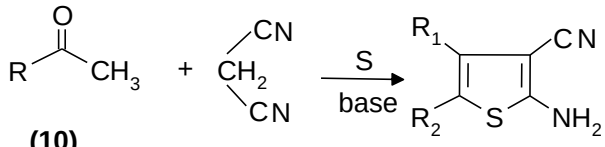
a) R_1=H , R_2 = CH_3

b) R_1 = OH, R_2 = H

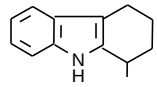
Structure of **(9a,b)** were confirmed by spectroscopic and elemental data.

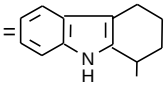
As an extension for the synthesis of the target compound (3-amino thienopyrimidine derivatives) the author focused on incorporating 2-aminothiophene 3-carbonitrile derivative **(11a,b)** with different reagents in the hope of obtaining compounds with different application.

Thus compound **(11a,b)** were obtained in good yield by reacting methyl 1,2,3,4-tetrahydrocarbazyl ketone[14] or methyl ethyl ketone **(10a,b)** with malononitrile and elemental sulfur in presence of morpholine as Gewald method reported[15].



(10) **(11)**

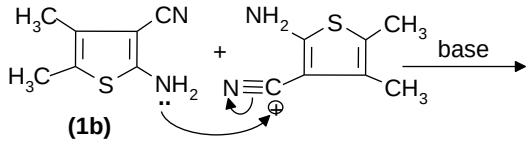
a) R =  b) R = C_2H_5

a) R_1 =  , R_2 = H

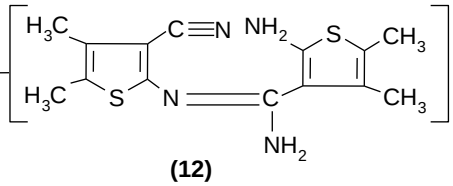
b) $R_1 = R_2 = CH_3$

Structure of **(11a,b)** were supported by spectroscopic and elemental data.

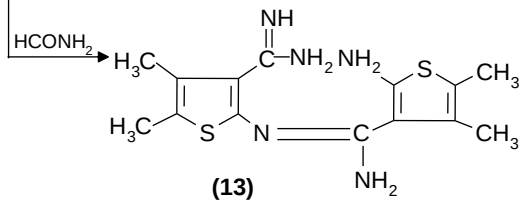
Interestingly bis derivative **(13)** was obtained by refluxing of 3-carbonitrile **(11b)** with formamide for 24 hours. The reaction proceeded via the self nucleophilic attack to form intermediate **(12)** which then formed the adduct derivative **(13).**



(1b)

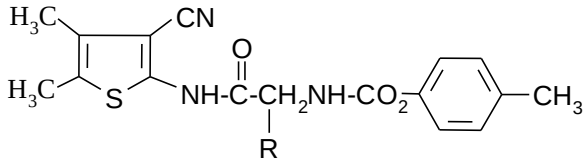


(12)



(13)

Similarly, thiophene enamino-3-carbonitrile **(11b)** reacted with acid chloride to give the corresponding amide derivatives **(14a-c).**



(14_{a-c})

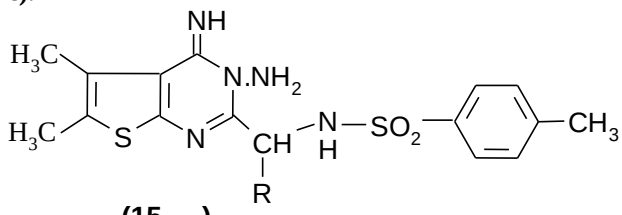
a) R = CH_3

b) R = $CH(CH_3)_2$

c) R = $CH(CH_3)C_2H_5$

Structure of derivatives (14a-c) were elucidated by IR, mass spectra and analytical data.

Similarly, interaction of cyanoamide derivatives **(14a-c)** with hydrazine hydrate in butanol caused cyclization to give 3-N-amino thieno [2,3-d] pyrimidin-4-imino derivative **(15a-c).**



(15_{a-c})

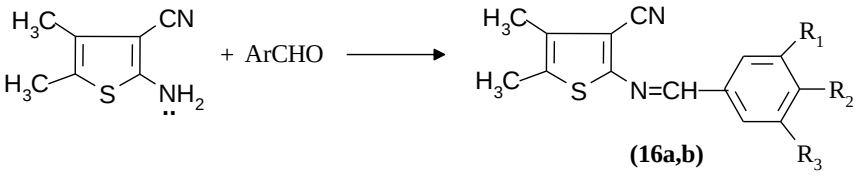
a) R = CH_3

b) R = $CH(CH_3)_2$

c) R = $CH(C_2H_5)CH_3$

The structures of **(15 a-c)** were established by IR, mass spectra and correct analytical data.

On the other hand, when **(11b)** was allowed to condense with different aldehydes namely 3,4,5-trimethoxybezaldehyde or N,N dimethyl-aminobenzaldehyde, it gave Schiff's bases **(16a,b).**

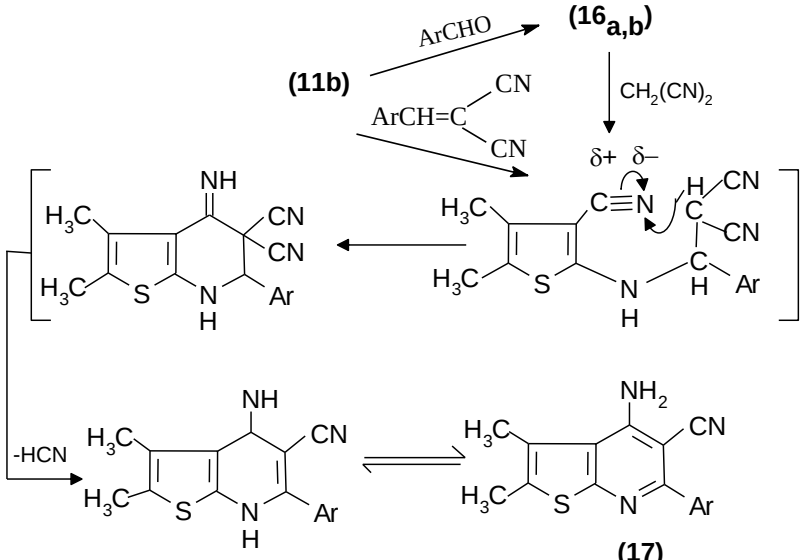


(16a,b)

a) R_1, R_2, R_3 = OCH_3

b) R_1,R_3 = H R_2 = $N(CH_3)_2$

Additionally when compounds **(16a,b)** were subjected to active methylene as malonoitrile, it underwent nucleophilic attack to yield the corresponding 4-amino-6-(aryl)-2,3-dimethyl-thieno [2,3-b] pyrimidin-5-carbonitrile through the formation of intermediate of Michael adduct which then cyclized and aromatized via loss one molecule of hydrogen cyanide to give **(17a,b)**. On the other hand compounds **(17a,b)** were also obtained directly by refluxing compound **(11b)** with benzylidine malononitrile in presence of triethylamine.



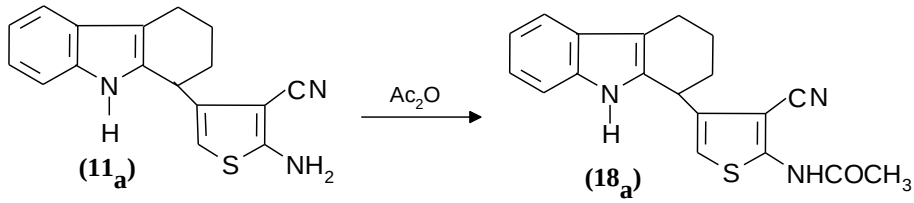
(17)

a) Ar = C_6H_2 $(OCH_3)_3$

b) Ar = C_6H_4 $N(CH_3)_2$

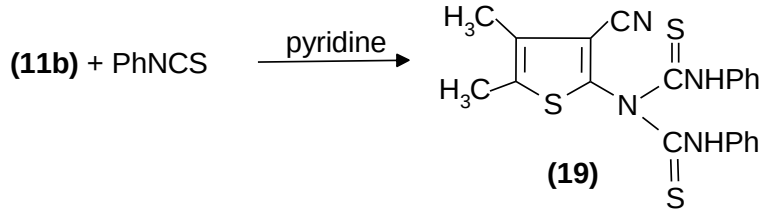
Structures **(17a,b)** were elucidated by correct elemental analysis and spectral data.

As an extension of these synthesis, Acetylation of carbonitrile derivatives **(11a)** with acetic anhydride consumed one mole of acetic anhydride to afford N-acetyl thiophen-3-carbonitrile derivative **(18)**



(11_a) **(18_a)**

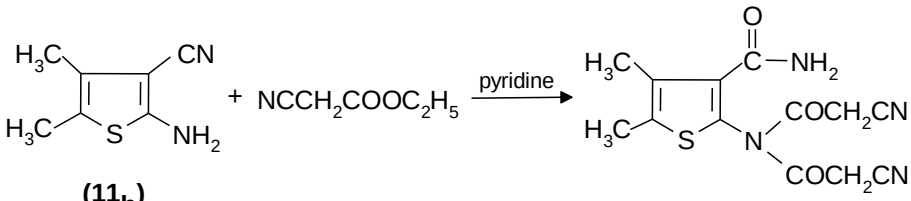
On the other hand, reaction of **(11b)** with phenyl isothiocyanate in presence of pyridine gave N,N-dithioamide derivative **(19)**.



(19)

Structure of **(19)** was confirmed by elemental and spectroscopic evidences.

Additionally condensation of **(11b)** with ethylcyanoacetate in pyridine as basic medium, consumed two moles of ethylcyanoacetate to give carboxamide derivative **(20).**



(11_b) **(20)**

Experimental

Melting points were uncorrected and were determined on a Stuart melting point apparatus. Elemental analyses were determined on a perkin Elmer, 240 (micro-analyses) Microanalytical laboratory, Cairo ,university, Giza, Egypt. IR spectra were recorded on a Shimadz 440 Infrared Spectrophotometer (Shimadzu) Japan using KBr technique . ^{1}H NMR Spectra were recorded on a BRUKER Proton NMR-Advance 300(300MHz)in DMSO-d_6 as a solvent , using tetra-methylsilane (TMS) as internal standard and chemical shift(δ)in ppm. Mass spectra were run on HP MODEL MS –5988.

Synthesis of 1-(4,5-dimethyl-3-carboxylate thiophen-2-carboxamido –2-yl) -1-methylmethyl or (2-methyl propyl or ethyl propyl)-4-methyl benzene sulphonamide. (3a-c) and Synthesis of 1-(4,5,6,7-tetrahydrobenzo-3-carboxylate thiophen-2-carboxamido –2-yl) -1-methylmethyl or (2-methyl propyl or ethyl propyl)-4-methyl benzene sulphonamide. (3d-f).

A mixture of *p*-tolyl-sulphonamido-N-1-(methyl or isopropyl or 2-butyl) acetyl chloride (0.01 mole) and Ethyl-(2-amino-4,5-dimethyl-thiophen-3-carboxylate **(1a)** (0.01 mole) or Ethyl-(2-amino-4,5,6,7-tetrahydro-benzothiophen)-3-carboxylate **(1b)** (0.01 mole) in dry diethylether was stirred vigorously for 12 hrs. The light brown solids were separated off, filtrated after evaporated of diethylether and recrystalized from ethanol to give **(3a-c)** and **(3d-f)** Table (3).

Compounds **(3a-f)** were confirmed by elemental analysis and spectroscopic evidences. Infrared spectra revealed absorption bands for –NH and C=O groups as shown in (Table 1).

Mass spectrum of **(3a)** exhibited a molecular ion peak at m/z 424 (M^+,30.02%), 379 (M^+–$3CH_3$) and other significant peak at 199 (100%), 153 (75%). Mass spectrum of **(3d)** exhibited a molecular ion peak at m/z 452 (M^+, 37%), 363 [M^+–88 ($COOC_2H_5$ + CH_3], with base peak at 199. Mass spectrum of (3d) exhibited a molecular ion peak at m/z 452 (M^+, 2.5%) and other significant peak at 450 (32.4%), 368 (1%) and a base peak at 199. ^{1}HNMR spectrum of **(3b)** in (**$CHCl_3$**) showed signals at δ 1.4-2 (m, 8H, tetrahydrobenzo), 2.4 (s,3H,CH_3–toluene–), 2.7 (d.d, 3H, CH_3–CH),4 (t, 3H, CH_3 (ester)), 4.5 (q, 2H, CH_2 (ester)), 5.2 (q, 1H, CH), 7.3 (m, 4H, Ar.H), 7.8 (s,1H,NH), 4.7 (s, 1H, OH, enol form). Mass spectrum of (3e) exhibited a molecular ion peak at m/z 478 (M^+, 36%) with a base peak at 225. Mass spectrum of **(3f)** exhibited a molecular ion peak at m/z 492 (M^+, 30%) with a base peak at 225.

Table(1):

Compound	$\upsilon_{max.}$ /cm^{-1}
3a	3147 (NH), 2977 (CH-aliphatic), 1658 (C=O).
3b	3186 (NH), 2962 (CH-aliphatic), 1651 (C=O).
3c	3448 (NH), 2970 (CH-aliphatic), 1651 (C=O).
3d	3139 (NH), 2931 (CH-aliphatic), 1658 (C=O).
3e	3201 (NH), 2931 (CH-aliphatic), 1651 (C=O).
3f	3263 (NH), 2931 (CH-aliphatic), 1666 (C=O).

Synthesis of N-[1-(3-amino-5,6-dimethyl-4-oxo-thieno-[2,3-d] pyrimidin -2-yl) 2-methyl methyl or (2-methyl propyl or 2-ethyl propyl)]-4-methyl benzene sulphonamide (4a-c) and N-[1-(3-amino-5,6,7,8-tetrahydrobenzo-4-oxo-thieno-[2,3-d] pyrimidin -2-yl) 2-methyl methyl or (2-methyl propyl or 2-ethyl propyl)]-4-methyl benzene sulphonamide (4d-f).

To solution of **(3a-c)** (0.01 mole) or **(3d-f)** (0.01mole)in n-butanol hydrazine hydrate (0.03 mole) was added, the mixture was refluxed for 8hrs. Filtered off washed with ethanol and recrystalized from ethanol to give **(4a-c)** and **(4d-f)** Table (3).

Structures **(4a-f)** were supported by elemental and spectral data. Infrared spectra revealed absorption bands for NH_2/NH and C=O groups as shown in Table II. ^{1}H-NMR spectrum (DMSO) of **(4a)** showed signals at δ 1.1 (d, 3H, CH_3–CH), 1.4, 2.1, 2.4 (3s, 9H, $3CH_3$) 5.2 (m, 1H,CH–), 7.0, 7.2 (2 dd, 4H, Ar-H), 8.2 (br. s, 1H, NH). Mass spectrum of **(4b)** revealed molecular ion peak of M^+ at m/z 420 (M^+, 8%), and other significant peaks at 377, 265, 222 with base peak at 91.

^{1}H-NMR spectrum of **(4b)** revealed signals at δ 8.1 ppm (2s, 6H, $2CH_3$), 2 (s, 3H, CH_3 (toluene), 2.4 (s, 6H, $2CH_3$), 5 (m, 1H, CH, isobutyl) 5.5 (d, 1H, CH-NH), 6.8-7.5 (2 dd, 4H, Ar-H), 7.8-8 (br-s,3H,NH/NH_2). ^{1}H-NMR spectrum (DMSO) of **(4c)** revealed a signals at δ 0.6-0.8 (2s, 6H, $2CH_3$), 1.4 (t, 3H, CH_3), 1.8 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2 (m, 1H, CH) 2.3 (s,3H,CH_3), 4.4 (d, 1H, CH), 7.2-7.7 (2d, 4H, ArH), 8.4 (s, 2H, NH_2). Mass spectrum of **(4d)** exhibited a molecular ion peak at 418 (M^+, 11%), and 263 (M^+ (SO_2–C_6H_4-CH_3) , and other peak at 155 with a base peak at 91.

Mass spectrum of **(4f)** exhibited a molecular ion peak at 460 (M^+, 1%), 458 (M^+–2%) and other significant peak at 384, 250, 227 with a base peak at 206.

Table(2):

Compound	$\upsilon_{max.}$ /cm^{-1}
4a	3301, 3209 (NH_2/NH), 2916 (CH-aliphatic), 1666 (C=O)
4b	3301, 3224 (NH_2/NH), 2962(CH-aliphatic), 1674 (C=O)
4c	3306, 3222 (NH_2/NH), 2960 (CH-aliphatic), 1670 (C=O)
4d	3402, 3301 (NH_2/NH), 2923 (CH-aliphatic), 1651 (C=O)
4e	3294, 3170 (NH_2/NH), 2854 (CH-aliphatic), 1651 (C=O)
4f	3325, 3186 (NH_2/NH), 2923 (CH-aliphatic), 1666 (C=O)

Ethyl-2-(2-aminoarylazo-1-naphthyl or 2-aminoarylazo-1-methylphenyl -4,5-dimethyl thiophen-3-carboxylate ester (6a-b).

Ethyl-2-amino-4,5-dimethyl thiophen-3-carboxylate ester **(1a)** (0.05 mole) was dissolved in solution of conc. hydrochloric acid (10 ml) with vigorous stirring and

cooling, cold solution of sodium nitrite (0.05 mole) was added gradually. The reaction mixture stirred for 2hrs at (0-5°C). The clear diazonium salt solution was slowly added to (0.05 mole) of *p*-toluidine or β-naphthylamine in acetic acid (50 ml) at 0°C, then further stirring for 5hrs. The dye formed was filtered, washed with water, dried and recrystalized from ethanol to give (6a,b) Table (3).

Structure of **(6a,b)** were supported by elemental analysis and spectroscopic data. Infrared spectrum of **(6a)** showed the presence of absorption bands at 3342, 3232 for NH_2 group and a band at 1778 for ester group. Infrared spectrum of **(6b)** showed absorption bands at 3400, 3248 (NH_2) 2978 (CH-aliphatic), 1716 (C=O) group, ^{1}H-NMR spectrum (DMSO) of **(6a)** revealed signals at δ 1 ppm (t, 3H, CH_3 ester), 1.3 (m, 6H, $2CH_3$ thiophene), 1.9 (s, 3H, CH_3 – toluene), 4.2 (m, 2H, CH_2 ester), 7-7.5 (m, 3H, Ar-H), 8.4 (s,2H, NH_2).

Ethyl-2-(N-aryl azo-3,4-dimethyl thiophen-3-carboxylate ($7_{a,b}$)

The clear diazonium salt solution *p*-toluidine (0.05 mole) or ethyl-2-amino-4,5-dimethyl thiophen-3-carboxylate ester **(5)** (0.05 mole) was slowly added to ethyl-2-amino-4,5-dimethyl thiophen-3-carboxylic ester **(1a)** (0.05 mole) in (20 ml) pyridine at (0-5)°C, then further stirring for 5hrs. The dye was filtered, washed with water dried and recrystalized from ethanol to give **(7a,b)** Table (3)**.**

The structures of **(7a,b)** were established according to spectroscopic and elemental analysis. Infrared spectrum of **(7a)** showed absorption band at 3308 (–NH), 1670 (C=O). Infrared spectrum of **(7_b)** showed absorption band at 3424 (NH), 1718 (O-C=O) of ester group**.** Mass spectrum of **(7b)** showed a molecular ion peak at m/z 410 (M^+, 20%) and base peak at 197. ^{1}H-NMR spectrum (DMSO) of **(7a)** revealed a signal at δ 1.1 (t, 3H, CH_3 ester), 1.3 (m, 6H, $2CH_3$-thiophene), 2.1 (s, 3H, CH_3-toluene), 4.2 (m, 2H, CH_2), 7-7.6 (m, 4H, Ar-H), 8.6 (s, 1H, NH).

***Synthesis of 2-N-(3-carboethoxy-4,5-dimethylthiophen-2-yl)-5-methyl benzo-[d]-1,2,3-triazol (8)*.**

A mixture of **(6a)** (0.01 mole) and cupper acetate (0.01 mole) in diethylformamide (20 ml) were refluxed for 4hrs. The reaction mixture was acidified with HCl, washed with water and filtered, recrystallized from ethanol to give **(8)**, Table (3).

The structure of derivative **(8)** indicated by the disappearance of NH_2 group and presence of ester group at 1718.

Ethyl-2-(1-hydroxy-4-methylphenyl or 1,3-dihydroxy phenyl) azo-4,5-dimethylthiophen-3-carboxylate ester (9a,b).

Ethyl 2-amino-4,5-dimethyl thiophen-3-carboxylate ester **(1a)** (0.05 mole) was dissolved in solution of conc. hydrochloric acid (10 ml) with vigorous stirring and cooling, cold solution of sodium nitrite (0.05 mole) in 10 ml water was added gradually. The reaction mixture stirred for 2hrs at 0-5°C. The clear diazonium salt solution was slowly added to (0.05 mole) of *p*-cresol or resorcinol in pyridine (20 ml) at 0°C further stirring for 5hrs. The dye formed was filtered, washed with water dried and recrystallized from ethanol to give **(9a,b)** Table (3).

Structures of derivatives **(9a,b)** were confirmed by the spectroscopic and elemental analysis data. Infrared spectrum of **(9a)** showed a broad band at 3318 (OH group), 2980 (CH-aliphatic), 1700 (o-c=o) Infrared spectrum of **(9b)** revealed absorption band at 3362 (OH group), 2980 (CH-aliphatic), 1704, (o-c=o) .^{1}H-NMR spectrum (DMSO) of **(9a)** showed signals at δ1 (t, 3H, CH_3 ester), 1.2 (m, 6H, $2CH_3$), 2.1 (s, 3H, CH_3), 4.2 (m, 2H, CH_2), 6.6-7.1 (2dd, 3H, Ar-H), 8.5 (s, 1H, OH), ^{1}H-NMR spectrum (DMSO) of **(9b)** revealed δ at 1.3 (br.m, 9H, $3CH_3$), 2.2 (s, 3H, CH_3), 4.3 (m, 2H, CH_2), 7.2 (m, 3H, Ar-H), 8.1, 8.9 (2s, 2H, 2OH).

Synthesis of 2-amino 4-(4,5,6,7-tetrahydrocarbazyl)-thiophen-3-carbonitrile (11a).

Mixture of methyl-1,2,3,4-tetrahydrocarbazyl ketone (0.01 mole), malnonitrile (0.01 mole), elemental sulphure (0.01 mole) and morphline (5ml) in ethanol (15ml) were refluxed for 4hrs. The solid obtained was filtered and recrystalized from ethanol as brown crystals (11a), Table (3).

Structures of **(11a,b)** were supported by spectroscopic and elemental analysis data.

Infrared spectrum of (11a,b) showed absorption bands at 3408, 3320, 3208 (NH_2/NH), 2206 (C≡N). Mass spectrum of (11a) exhibited a molecular ion peak at m/z 293 (M^+, 10%), Infrared spectrum of (11b) showed absorption bands at 3363, 3218 (–NH_2), 2930 (CH–aliphatic), 2222 (C≡N), Mass spectrum of (11b) exhibited a molecular ion peak at m/z 152 [(M^++1) 100%], ^{1}H-NMR spectrum (DMSO) of (11b) revealed signales at 1.9, 2.1 (2s, 6H, $2CH_3$), δ 6.8 (s, 2H, NH_2).

Synthesis of 2-[(2-amino-4,5-dimethyl thiophen-3-yl) imidoyl amino]-4,5-dimethyl thiophen-3-carboxamidine (13).

Compound **(11b)** (0.01 mole) in formamide (25ml) was refluxed for 24hrs. the reaction mixture allowed to stand at room temp., filtered and reycrystalized from ethanol to form compound **(13)** as dark brown crystals Table (3).

The structure of **(13)** was confirmed by correct analytical and spectral data. Infrared spectrum indicated the absence of cyano group and presence of NH_2/NH group at absorption bands at 3430,3322, 3132cm^{-1}. Mass spectrum exhibited a molecular ion peak at m/z 320 (M^+-1, 10%), 260 (M^+– $4CH_3$) and other peaks at 216, 144.

Synthesis of 1-(4,5-dimethyl-3-carbonitrile thiophen-2-carboxamido –2-yl) -1-methylmethyl or (2-methyl propyl or ethyl propyl)-4-methyl benzene sulphonamide. (14_{a-c})

A mixture of compound **(11b)** (0.01 mole), *p*-tolyl sulphonamide N-(methyl or isopropyl or 2-butyl) acetyl chloride in diethylether stirred vigorously for 12 hrs. The brown solids were separated off, filtrated after evaporating diethylether and recrystalized from ethanol to give **(14a-c)**, (Table 3).

The structure of derivatives **(14a-c)** were elucidated by the correct analytical data. Infrared spectrum of **(14a)** showed absorption band at 3194 for –NH group, 2924 for –CH aliphatic, a band at 2192 which indicated the presence of C≡N group and finally band at 1686 due to the presence of C=O group. Also, infrared spectrum of **(14b,c)** indicated the presence of NH- group at 3236, 3226, and absorption bands at 1682, 1694 for C=O group. Mass spectrum of **(14a)** exhibited a molecular ion peak at m/z 377 (M^+, 25%), 222 (M^+–H_3C–C_6H_4-SO_2), and other peaks at 153 and 91. Mass spectrum of **(14b)** showed a molecular ion peak at m/z 406 (M^+ + 1, 50%) and other significant peaks at 332, 225 with abase peak at 180. Mass spectrum of **(14c)** exhibited a molecular ion peak at m/z 418 (M^+-1), 405 (M^+-CH_3), and other significant peaks at 226, 152.

Synthesis of N-[1-(3-amino-5,6-dimethyl-4-oxo-thieno-[2,3-d] pyrimidin -2-yl) 2-methyl methyl or (2-methyl propyl or 2-ethyl propyl)]-4-methyl benzene sulphonamide ($_{15a-c}$).

To solution of **(14a-c)** (0.01 mole) in n-butanol, hydrazine hydrate (15ml , 0.03 mole) was added, the mixture was refluxed for 8hrs. Filtered off washed with ethanol and crystalized from ethanol to give **(15a-c)** Table (3).

The structures of **(15a-c)** were demonstrated by IR, mass and correct analytical data. Infrared spectrum **(15a)** showed the disappearance of cyano group which found in the parant compound and appearance of bands at 3338, 3276, (NH_2). Infrared

spectrum of **(15b)** showed abroad band at 3410, 3334, 3246 (NH/NH_2), disappearance of C≡N. group. Mass spectrum of **(15b)** exhibited a molecular ion peak at 420 (M^+ + 1), 377 (M^+–$CH(CH_3)_2$) with other significant peaks at 222,155,91. Infrared spectrum of **(15c)** showed absorption bands at 3355, 3263 (NH/NH_2) with disappearance of C ≡ N group.

Synthesis of 2-N-[3,4,5-trimethoxy phenyl or N,N-dimethyl phenyl amino ethylidene-4,5-dimethyl thiophen-3-carbonitrile (16a,b)

A mixture of compound **(11b)** (0.01 mole) and different aldehydes (e.g.:3,4,5-trimethoxybenzaldehyde or N,N-dimethyl-*p*-aminobenzalde-hyde) (0.01 mole) in ethanol (20 ml) and drops of triethylamine was refluxed for 6hrs. After cooling and acidification with HCl, the ppt is washed with H_2O and recrystalized from ethanol to give **(16a,b)**, Table 3.

The structure of **(16a,b)** were confirmed by the disappearance of $–NH_2$ bands and presence of cyano group in infrared spectra. Infrared spectrum of **(16a)** showed no absorption band for $–NH_2$, 2222 for C≡N group.

Synthesis of 4-amino-2,3-dimethyl-6-(3,4,5-trimethoxyphenyl or N,N-dimethylaminophenyl) thieno[2,3-b] pyridin-5-carbonitrile (17a,b).

A mixture of **(11b)** (0.01 mole) and different arylidine derivative (e.g.: 3,4,5-trimethoxy benzylidine malononitrile or N, N-dimethyl-*p*-amino benzylidine malononitrile) (0.01 mole) in ethanol (20 ml) in presence of T.E.A. (5 ml) was refluxed for 6-8 hrs, after cooling and acidification with HCl, the ppt formed was collected by filteration, washed with H_2O and recrystallizated from ethanol to give **(17a,b)**, Table (3).

Structures of **(17a,b)** were elucidated by correct elemental analysis Table 3. Infrared spectra revealed the presence of $–NH_2$ and C≡N group. Infrared spectrum of **(17a)** showed absorption bands at 3304, 3212, (NH_2), 2926 (CH-aliphatic), 2926 (CH-aliphatic), 2220 (C≡N). Infrared spectrum of **(17b)** revealed absorption bands at 3306, 3212 (NH_2), 2926 (CH–aliphatic), 2218 (C≡N). Mass spectrum of **(17a)** exhibited a molecular ion peak at m/z 369 (M^+, 50%). ^{1}H-NMR spectrum (DMSO) of **(17a)** revealed the signals at 2.2 (s,3H, CH_3), 2.5 (s, 3H, CH_3), 3.5 (s, 6H, $2OCH_3$), 3.9 (s, 3H, OCH_3), 7.3 (d, 2H, Ar-H) 7.9 (s,1H,NH_2). Mass spectrum of **(17b)** showed a molecular ion peak at m/z 322 (M^+, 20%).

2-N-acetyl-4-(1,2,3,4-tetrahydrocarbazyl) thiophen-3-carbonitrile (18).

Compound **(11a)** (0.01 mole) in acetic anhydride (20 ml) was refluxed for 4-hrs. The reaction mixture allowed to cool at room temperature, filtered and recrystalized from ethanol to give **(18).** Compound **(18)** was obtained 60% yield as pale brown crystals Table (3).

Infrared spectrum **(18)** showed bands at 3422, 3232 (2-NH), 2913 (CH-alliphatic), 2222 (C≡N), 1700 (C=O). Mass spectrum showed a molecular ion peak at 335 (M^+, 8%), and other peaks at 287, 229 and 77,

2-N,N-diphenyl thioamido-4,5-dimethyl thiophen-3-carbonitrile (19).

A mixture of compound **(1b)** (0.01 mole) and phenyl isothiocyanate (0.01 mole) in pyridine (25 ml) were refluxed for 8 hrs. the reaction mixture was acidified with HCl, washed with H_2O then filtered, crystallized from ethanol to give **(19)**, as dark crystals (Table 3).Infrared spectrum showed absorption band at $\upsilon_{max.}$ 3334cm^{-1} (–NH), 2922 (CH-aliphatic), 2212 (C≡N), 1242, 1216 (C=S) Mass spectrum revealed a molecular ion peak at m/z 422 (M^+, 10%) 407 (M^+–CH_3), 287 (CS-NHC_6H_5) with abase peak at 77.

2-N,N-dicyanoacetyl-amino-3-carboxamido-4,5-dimethyl thiophene (20)

A mixture of compound **(11_b)** (0.01 mole) and ethylcyanoacetate (0.02 mole) in pyridine (20 ml) was refluxed for 12 hrs. after cooling and acidification with HCl, ppt is washed with H_2O and recrystalized from ethanol to give **(20)** , as dark crystalles Table (3).

The structure of **(20)** was supported with correct elemental analysis and spectral data. Infrared spectrum showed a broad band at 3448, 3328 (NH_2 group), 2928 (CH-aliphatic), 2216,2216 (C≡N), 1654, 1716 (C=O groups), Mass spectrum of **(20)** illustrated a molecular ion peak at 304 (M^+, 25%) with a base peak at 151.

Pharmacological Studies

Analgesic activity

The hot plate method (Jacobs and Bossowki)[16] was used for studying the analgesic activity 42 rats of both sexes were divided into 7groups, six rats each. one of these groups was kept as control while 5 of these groups given 10 mg /kg of the different compound the last group given 5 mg Novalgin After treatment , Rats were placed in hot plate (U Go Basil E) at 50 C°. The reaction time was measured at 1

and 2 hours. The results were calculated, statistically analysed and compared with these of control group using student t- test.

Anti convulsant effect of the tested compounds were determined according to Vemadakis[17] and wood burgy Electrical stimulation was applied to the rat ear using master schocker (E ct unit U Go. Basile) . Groups of animals received 10 mg / kg of each of the tested compound. Carbamazapin was used as positive control . percent increase in voltage (mA) required to induce an electric shock in treated animals as compared to the control group was taken as a measure of anticonvulsant activity.

Anti inflammatory effect (carrageenan induced rat paw edema)

This effect was determined according to the method, described by Winter et al[18]. Rats were divided into seven groups each of six rats , paw oedema was induced by injecting 0.1 ml of 1% solution of sterile carrageenan Lambda in saline into right hind paw of the rat. The rats received vehicle (1 ml saline / 100 gin) or the tested compounds 10 mg / kg of each orally one hour before carrageen an injection. Four hours after the carrageen an injection paw volume (ml) was measured with a plethysmometer (21025 comerio (Av) Italy) . Results are expressed as a percent change from control values.

$$\frac{\text{vol. of right paw} - \text{vol. of left paw}}{\text{vol. of left paw}} \times 100$$

Analgesic Effect (Hot Plate)

Compound	Dose mg/kg.	Mean values of the reaction time after treatment	
		1 h x ± S.E.	2 h x ± S.E.
Control	1 ml saline	62.5 ± 6.5	66.5 ± 4.2
4a	10	54.0 ± 3.3	56.0 ± 5.1
4b	10	96.7 ± 3.4**	58.8 ± 4.2
4c	10	106.2 ± 2.9**	92.2 ± 4.7**
4d	10	90.5 ± 7.1**	88.7 ± 5.8**
4e	10	76.2 ± 3.1**	48.0 ± 1.5
Novalgin	5	120 ± 1.7***	126 ± 1.5***

* Significant at P≤ 0.05 vs control group

** Significant at P≤ 0.01 vs control group

*** Significant at P≤ 0.001 vs control group

Electric convulsive threshold in adult male rats after administration of single oral dose (10 mg/kg)

Comp	Dose	60 min x ± S.E.	Electric convulsive threshold (mA)				
			% increase	120 min x ± S.E.	% increase	180 min x ± S.E.	% increase
Control	--	2.5 ± 0.4	--	3.2 ± 0.2	--	2.7 ± 0.2	--
4a	--	5.8 ± 0.6**	132	4.7 ± 0.7*	46.9	3.5 ± 0.5	29.6
4b	--	5.6 ± 0.6**	124	4.8 ± 0.6	50	3.7 ± 0.4	370
4c	--	5.0 ± 0.6**	100	3.3 ± 0.3	3.1	3.8 ± 0.3	40.7
4d	--	43. ± 0.7*	72	3.3 ± 0.3	3.0	3.8 ± 0.5	40.7
4e	--	3.5 ± 0.6	40	2.8 ± 0.2	-12.5	3.6 ± 0.5	33.3
Carbamazapin	100	7.8 ± 0.8**	212	8.1 ± 0.8**	153.1	8.2 ± 0.7	203.7

* Significant at P≤ 0.05 vs control group
** Significant at P≤ 0.01 vs control group

Acute anti-inflammatory effect of the tested compounds on carrageen an induce rat paw aedema

Comp	Dose Mg/kg	% oedema m ± S.E.					
		1h /sign.	% edema inhibition	2 h	% edema inhibition	3 h	Edema inhibition
Control	1 ml saline	57.3 ±5.1	0	50.6 ±6.0	--	40.4 ±4.9	--
4a	10	21.2± 2.2***	62	18.5 ±1.9***	63.4	25.2 ±2.5*	37.6
4b	10	14.8±2.1***	74.2	23.5 ±3.3***	53.6	28.0 ±3.4	30.7
4c	10	21.3±2.5***	62.8	28.7 ±3.7***	43.3	44.1 ±2.5	9.2
4d	10	10.9±4.1***	81.0	31.5 ±1.8***	37.7	33.2 ±2.5	17.8
4e	10	20.3±1.9**	64.6	32.6 ±0.5*	35.6	43.2 ±4.0	6.9
Carbamazapin	20	10.4±1/9***	81.8	10.5 ±1.0***	79.2	9.2 ±1.1	77.2

* Significant at P≤ 0.05 vs control group.
*** Significant at P≤ 0.001 vs control group.

Table (3)

Comp. No.	M.P. (C°)	Yield % colour	Molecular formula	Analysis % Required/Found			
				C	H	N	S
3a	166	40% Brown	$C_{19}H_{24}N_2O_5S_2$ (424.51)	53.75 53.77	5.69 5.70	6.59 6.62	15.10 15.12
3b	170	43% Brown	$C_{21}H_{28}N_2O_5S_2$ (452.51)	55.73 55.75	6.23 6.25	6.19 6.21	14.16 14.18
3c	140	47% Brown	$C_{22}H_{30}N_2O_5S_2$ (466.50)	56.63 56.65	6.48 6.50	6.00 6.02	13.74 13.76
3d	190	46% Brown	$C_{21}H_{26}N_2O_5S_2$ (450.54)	55.98 56.00	5.81 5.83	6.21 6.23	14.23 14.25
3e	170	48% Brown	$C_{23}H_{30}N_2O_5S_2$ (478.55)	57.72 57.74	6.31 6.33	5.85 5.87	13.39 13.41
3f	140	50% Brown	$C_{24}H_{32}N_2O_5S_2$ (492.58)	58.51 58.53	6.54 6.56	5.68 5.70	13.01 13.03
4a	180	30% White	$C_{17}H_{20}N_4O_3S_2$ (392.47)	52.02 50.04	5.14 5.16	14.27 14.29	16.33 16.35
4b	185	33% White	$C_{19}H_{24}N_4O_3S_2$ (420.52)	54.26 54.28	5.75 5.77	13.32 13.34	15.24 15.26
4c	165	37% White	$C_{20}H_{26}N_4O_3S_2$ (434.52)	55.27 55.29	6.03 6.05	12.89 12.91	14.75 14.77
4d	220	36% White	$C_{19}H_{22}N_4O_3S_2$ (418.48)	54.52 54.54	5.29 5.31	13.38 13.40	15.32 15.34
4e	190	38% White	$C_{21}H_{26}N_4O_3S_2$ (446.53)	56.48 56.50	5.86 5.88	12.54 12.56	14.35 14.37
4f	174	40% White	$C_{22}H_{28}N_4O_3S_2$ (460.56)	57.36 57.38	6.12 6.14	12.16 12.18	13.92 13.94
6a	140	75% Reddish	$C_{16}H_{19}N_3O_2S$ (317.39)	60.54 60.56	6.03 6.05	13.24 13.26	10.10 10.13
6b	150	74% Brownish red	$C_{19}H_{19}N_3O_2S$ (353.42)	64.56 64.58	5.41 5.43	11.89 11.91	9.07 9.09
7a	130	75% Orange	$C_{16}H_{19}N_3O_2S$ (317.39)	60.54 60.56	6.03 6.05	13.24 13.26	10.10 10.12
7b	145	74% Violet	$C_{18}H_{23}N3O_4S_2$ (409.50)	52.79 52.81	5.66 5.68	10.26 10.28	15.65 15.67
8	290	90% Brown	$C_{16}H_{17}N_3O_2S$ (315.37)	60.93 60.95	5.43 5.45	13.32 13.34	10.16 10.18

Table 3 cont.

9_a	160	75% reddish blue	$C_{16}H_{18}N_2O_3S$ (318.36)	60.36 60.38	5.69 5.71	8.80 8.82	10.07 10.09
9b	165	74% Reddish	$C_{15}H_{16}N_2O_4S$ (320.34)	56.24 56.26	5.03 5.05	8.74 8.76	10.08 10.10
11a	200	60% Brown	$C_{17}H_{15}N_3S$ (293.37)	69.59 69.61	5.15 5.17	14.32 14.34	10.92 10.94
13	>300	80% Dark brown	$C_{14}H_{19}N_5S_2$ (321.44)	52.30 52.32	5.95 5.97	21.78 21.80	19.94 19.96
14_a	190	40% Yellowish brown	$C_{17}H_{19}N_3\ O_3S_2$ (377.43)	54.09 54.10	5.07 5.09	11.13 11.15	16.98 17.01
14_b	224	42% Yellowish brown	$C_{19}H_{23}N_3O_3S_2$ (405.51)	56.27 56.29	5.71 5.73	10.36 10.38	15.81 15.83
14_c	200	43% Brown	$C_{20}H_{25}N_3O_3S_2$ (419.53)	57.25 57.27	6.00 6.02	10.01 10.03	15.28 15.30
15_a	240	40% White	$C_{17}H_{21}N_5O_2\ S_2$ (391.49)	52.15 52.17	5.40 5.42	17.89 17.91	16.37 16.39
15_b	270	42% White	$C_{19}H_{25}N_5O_2S_2$ (419.54)	54.39 54.41	6.00 6.02	16.69 16.71	15.28 15.30
15_c	260	43% White	$C_{20}H_{27}N_5O_2S_2$ (433.57)	55.40 55.42	6.27 6.29	16.15 16.17	14.78 14.80
16_a	160	80% pale green	$C_{17}H_{18}N_2O_3S$ (330.36)	61.79 61.81	5.49 5.51	8.47 8.49	09.70 09.72
16_b	170	70% Brown	$C_{16}H_{17}N_3S$ (283.37)	67.81 67.83	6.04 6.06	14.82 14.84	11.31 11.33
17_a	190	75% Green	$C_{19}H_{19}N_3O_3S$ (369.42)	61.76 61.78	5.18 5.20	11.37 11.39	08.67 08.68
17b	200	74% Brown	$C_{18}H_{18}N_4S$ (322.41)	67.05 67.07	5.62 5.64	17.37 17.39	09.94 09.96
18	210	60% Pale brown	$C_{19}H_{17}N_3OS$ (335.1)	68.03 68.05	5.11 5.13	12.52 12.54	09.55 09.57
19	>300	70% dark brown	$C_{21}H_{18}N_4S$ (422.56)	59.68 59.70	4.29 4.31	13.25 13.27	22.76 22.78
20	>300	80% dark brown	$C_{13}H_{12}N_4O_3S$ (304.31)	51.31 51.33	3.97 3.99	18.41 18.43	10.53 10.55

References

1. SHISHOO C.J, DEVANI M.B., ULLAS G.V., ANANTHAN S., AND BHADTI V.S., J. Heterocyclic Chem., 22, 825 (1985).
2. JAMES D.M., AND REES A..H., J. Med. Pharm. Chem., 5, 1234 (1962).
3. WERENER L.H., RICCO S.A.., AND DESTEVENS G., J. Med. 10, 575 (1967).
4. Barsky L.I., and Benze W.L., J. Med. 14, 40 (1971).
5. GRONOWITING S., ROOSM S., SJOBERG B., AND STJERNSTORM N.E., Acta Pharmcsecica, S, 563 (1968).
6. DEVANI M.B., SCHISHOO C.J., PATHAK U.S., SHARMA B.G., AND PADHYA A. C., Indian J. Chem., 15B (6), 575, (1977).
7. EL-SHERBENY M.A.., EL-ASHMAWY M.B., EL-SUBBAGH H.I., EL-EMAM A..A.., AND BADRIA F.A.., Eur. J. Med. Chem. 30(5), 445, (1995).
8. NICLSEN, K.E., AND PEDERSEN E.B., Cjemica Sceopta. 18135 (1981).
9. PATHAK M.S., PARIKN S.H., SHAH G., AND PADLYA A..C., J. Pharm. Sci., 65 (5), 660 (1976).
10. CHAMANAL J.S., VIKAS S.S., ISHWARSINH S.R., VIKAS D.Y., Eur. J. Med. Chem. 35, 351-358 (2000).
11. TINNEY F.J., AND CETENKO W. J., J.Med.Chem.24,878(1981) .
12. MANHAS M.S., SHARMA S. D., AND AMINE S.G., J. Med. Chem.15,106(1972).
13. SABINS R.W., AND RANGNEKAR D.W., J. Heterocyclic 27, 417 (1990).
14. SHMEISS N.A..M.M, ISMAIL M.M.F., SOLIMAN A..M., EL-DIWANI H.I. Molecules 5, 1101-1112, (2000).
15. GEWALD K., SCHINKE E., AND BOTLCHER H., Chem. Ber., 99, 94 (1966).
16. JACOBS W.A.., AND BOSSOWKI M., Arch –inter-Pharmacodyn. 133, 296, (1961).
17. VERNADAKIS A.., AND WOOD BURGY D.M., J. Pharmacol. Exp. Therap. , 148, 144 (1965).
18. RISLEY E.A.., AND NUS G.W., Proc. Soc. Exp. Biol. Med., 111, 3. 455-456 (1962).

الملخص العربى

التحضير والتأثير البيولوجى لبعض مركبات ثينو [2,3-d] بيرميدين-4-(3H) أون

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تفاعل الثيوفين انمينو استر (1a,b) مع مشتقات كلوريد الحمض لباراتوليل سلفوناميد –N– مشتقات حمض الخليك (2a-c) ينتج الأميد المقابل (3a-f). ويتفاعل مشتقات الأمين 3a-f مع الهيدرازيد هيدرات ينتج (4a-f) . ومن دستزة المركب (1a) أعطى مركب 5 الذى تفاعل مع أمينات مختلفة ليعطى (7a,b) فى وجود البيريدين فإنه يعطى مركب 7a,b وفى وجود ملح أسيتات النحاس تحدث اكسدة هوائية للمركب 7a ليعطى مركب (8) ويتفاعل (5) مع فينولات مختلفة يعطى المركب (9a,b). وعند تفاعل ديازينوم كلوريد للباراتولودين أو الديازنيوم كلوريد للمركب (1).

وقد أمكن الحصول على مشتقات آخرى من أمينو ثينوبيرميدين بطريقة Gewald للحصول على 11a,b ومن المركب 11a,b أمكن الحصول على المركبات 20, 19,18,17a & b, 15a-c,14a-c,13

وقد تم اثبات تركيب المركبات التى تم الحصول عليها بواسطة الأشعة تحت الحمراء ومقياس الكتلة والرنين المغناطيسى.

وبدارسة التاثير البيولوجى لبعض المشتقات الجديدة وجد أن لها تأثير فارماكولوجى كمضاد للحساسية والإلتهابات والتشنجات. وبإجراء المسح الميكروبيولوجى لعدد من المشتقات الجديدة كمضادات للميكروبات على أنواع مختلفة من البكتريا أتضح أن بعضها له تأثير فعال كمضاد للفطريات.