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Pyrimidine Derivatives Containing Sulfaphenazole and Sulfadimethoxine Moieties with Antitumor Activity

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Abstract: 4-Amino-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide(sulfaphenazol) and sulfadimethoxine (**2a,b**) were selected as starting materials for the synthesis of some novel hydroquinoline, pyrimidoquinoline and pyrimidine derivatives to evaluate the antitumor activity. Pyrimidine did prove to have antineoplastic activity and it is now valuable drugs for treatment of tumors of the breast, colon or rectum and to a lesser extent, gatric, hepatic, pancreatic, uterine, overian and bladder carcinomas.

Key words: Hydroquinoline · Pyrimidoquinoline · Antitumor activity

INTRODUCTION

The chemistry of pyrazole[1] and hydroquinoline derivatives have increasing interest since many of these compounds have found useful applications as chemotherapeutic agents against malaria [2-4], parasites and microbes [5, 6]. Pyrazole derivatives are important class of heteroaromatic ring system that finds extensive use in the pharmaceutical industry [7]. Pyrazole derivatives are reported to show antibacterial [8, 9], antifungal [10] and anticancer agents [11]. Furthermore it was found that pyrazole derivatives act as intermediates for agricultural microbicides and herbicides [12]. In view of the above mentioned findings and in continuation of our work in biologically activity of this class of compounds [13-19] and evaluating their antitumor activity in a trial of obtaining new compounds with high antitumor activity and less toxicity. Herein we report the synthesis of some novel pyrimido [4, 5-b] quinoline derivatives and evaluating antitumor activity [20-22].

MATERIALS AND METHODS

Melting points were determined on Buchi melting point apparatus (B-540). Elemental analyses were determined on a Perkin Elmer 240 (microanalyses) of Microanalytical unit, Cairo University, Giza, Egypt. IR spectra were recorded on a Shimadzu 440 Infrared Spectrophotometer (Shimadzu) Japan using KBr disk technique (υ, cm^{-1}). ^1H NMR Spectra were recorded on a BRUKER Proton NMR-Avance 300 (300MHz), in DMSO-d_6 as a solvent and the chemical shifts are given in δ (ppm) downfield from tetramethylsilane as internal standard. Mass spectra were run on HP MODEL MS – 5988, 700v (Japan) and compound **4** was prepared as literature.

Preparation of Compounds (3a, b): General Procedure: A mixture of dimidone (5,5-dimethyl-1,3-cyclohexadione) **1** (0.01 mol), sulpha-phenazole (4-amino-N-(1-phenyl-1H-pyrazol-5-yl)-benzene sulfonamide (0.01 mol) or sulphadimethoxine (4-amino-N-(2,6-dimethoxypyrimidin-4 yl)benzenesulfon-amide **2a,b** (0.01 mol) and absolute ethanol (30 mL) was refluxed for 5hr. The reaction mixture was cooled, diluted with water and the resulting solid was filtered off, air dried and crystallized from ethanol to give **3a, b** (**Scheme 1**).

4-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)-N-(1-phenyl-1H-pyrazol-5-yl)-benzenesulfonamide(3a): Yield 90%; Mp. 120-122°C; IR: 3364, 3228 (NH), 3060 (CH arom.), 2957 (CH-aliph.), 1632 (C=O), 1108, 1380 (N-SO_2). MS: *m/z* (%) 437 (M^++1, 0.66), 314 (7.62), 250 (7.18), 223 (0.58), 156 (45.10), 108 (51.40), 52 (100). Anal. Calcd. for $C_{23}H_{24}N_4O_3S$ (436); C, 63.28; H, 5.54; N, 12.83%. Found: C, 63.61; H, 5.32; N, 12.60.

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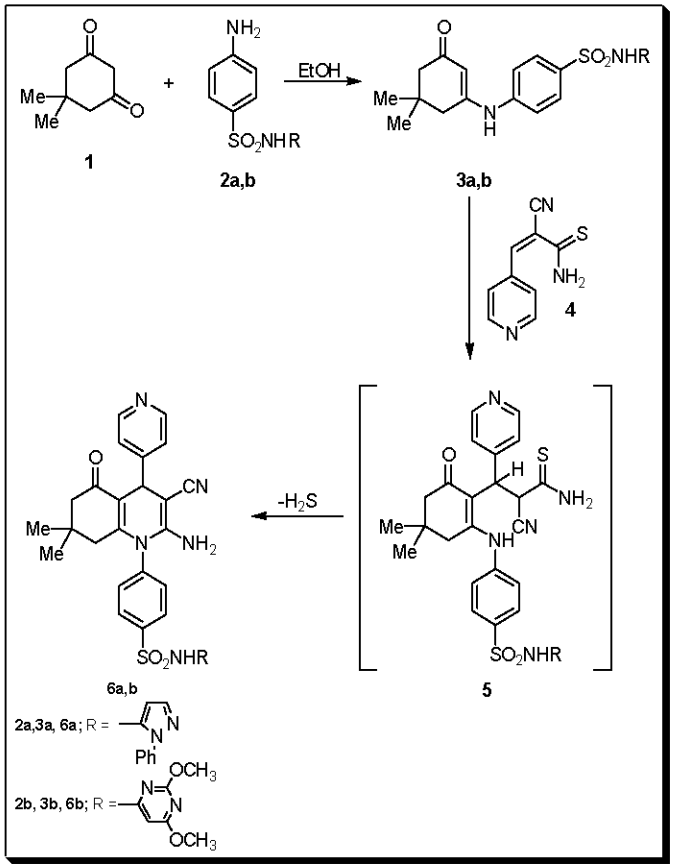


Scheme 1:

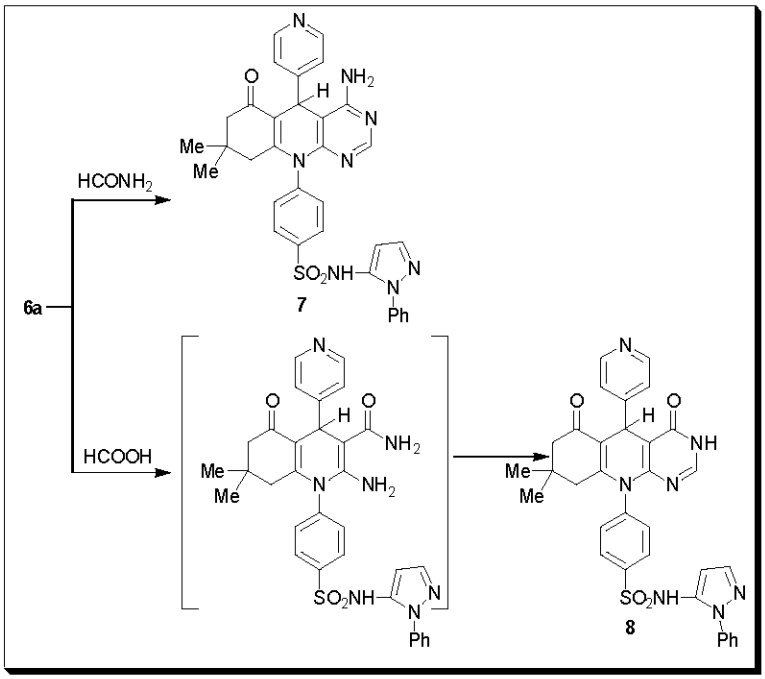
N-(2,6-Dimethoxypyrimidin-4-yl)-4-(5,5-dimethyl-3-oxocyclohex-1-enylamino)-benzenesulfonamide (3b): Yield: 90%; Mp. 170-172°C; IR: 3385, 3215 (NH), 3087 (CH arom.), 2926 (CH-aliph.), 1632 (C=O), 1159, 1380 (N-SO_2). MS: *m/z* (%) 432 (M^+, 1.2), 386 (2.08), 274 (2.34), 224 (3.90), 158 (4.55), 129 (4.16), 52 (100). Anal.Calcd. for $C_{20}H_{24}N_4O_5S$ (432); C, 55.54; H, 5.59; N, 12.95%. Found: C, 55.32; H, 5.34; N, 12.74.

General method for preparation of compounds 6 a, b: A mixture of **3a, b** (0.01 mol), by filtration 4-pridinylidenethiocyanoacetamide **4** (0.01 mol) and piperidine (3 drops) in ethanol (30 mL) was refluxed for 7hr. The solid obtained upon cooling was collected by filtration and crystallized from ethanol to give **6a, b** (**Scheme 1**).

4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-quinolin-1(4H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (6a): Yield: 66%; Mp. 278-280°C; IR: 3412, 3302 (NH_2), 3095 (CH-arom.), 2218 (C=N), 1649 (C=O) and 1115, 1229 (N-SO_2). MS: *m/z* (%) 591 (M^+, 3.85), 437 (2.71), 308 (3.17), 185 (6.56), 129 (13.12), 69 (100). Anal. Calcd. for $C_{32}H_{29}N_7O_3S$ (591.68); C, 64.96; H, 4.94; N, 16.57%. Found: C, 64.62; H, 4.76; N, 16.84.

4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-quinolin-1(4H)-yl)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide(6b): Yield: 60%; mp. 240-242°C; IR: 3410, 3303 (NH_2), 3097 (CH arom.), 2219 (C=N), 1650 (C=O) and 1117, 1217 (N-SO_2). MS: *m/z* (%) 587 (M^+, 1.42), 467 (3.36), 391 (13.2), 368 (11.38), 313 (6.66), 183 (5.76), 122 (2.13), 88 (100). Anal. Calcd. for $C_{29}H_{29}N_7O_5S$ (587.20); C, 59.27; H, 4.97; N, 16.68%. Found: C, 59.43; H, 5.13; N, 16.56.

4-(4-Amino-8,8-dimethyl-6-oxo-5-(pyridin-4-yl)-6,7,8,9-tetra-hydropyrimido[4,5-b]quinolin-10(5H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (7): A solution of **6a** (0.01 mol) in formamide (10 mL) was refluxed for 5h. The solid obtained by filtration was crystallized from dioxane to give **7**. Yield: 80%; mp. 300-302°C;



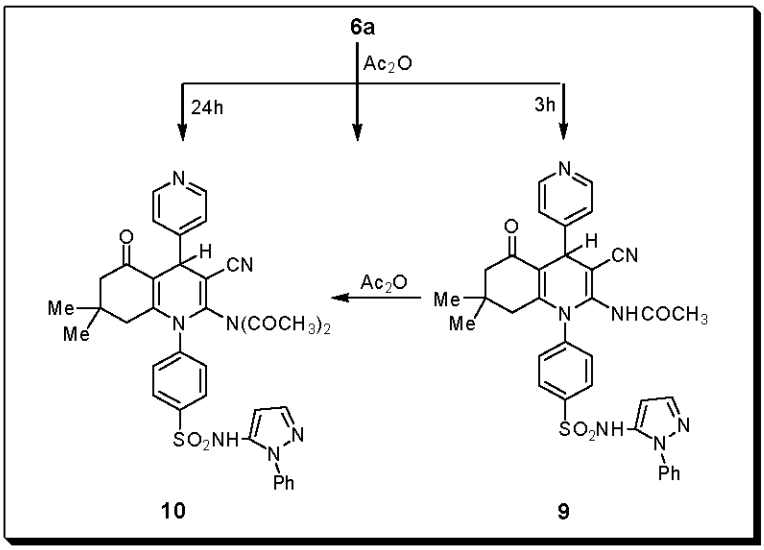
Scheme 2:

IR: 3399, 3225 (NH_2), 3023 (CH-arom.), 2926 (CH-aliph.), 1682 (C=O), 1242 (N-SO_2). ^{1}HNMR: 1.21, 1.85 (2s, 6H, $2CH_3$), 2.11,2.51 (2s, 4H, $2CH_2$ cyclo), 4.1 (d, 5H, pyridine-H), 6,74(s,1H,CH-pyrimidine), 7.96-7.53 (m, 9H, Ar-H), 8.03-8.17 (d, 2H, pyrazole-H), 8.36 (s, 2H, NH_2), 10.36 (s, H, $NHSO_2$). MS: *m/z* (%) 618 (M^+, 25.8), 396 (8.8), 354 (7.9), 339 (100), 314 (2.4), 77 (34.8). Anal. Calcd. for $C_{33}H_{30}N_8O_3S$ (618); C, 64.06; H, 4.89; N, 18.11%. Found: C, 64.24; H, 4.64; N, 18.32.

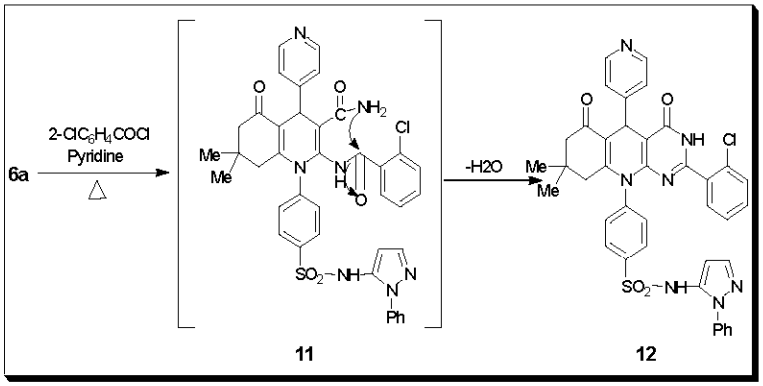
4-(8,8-Dimethyl-4,6-dioxo-5-(pyridin-4-yl)-3,4,6,7,8,9-hexa-hydropyrimido[4,5-b]quinolin-10(5H)-yl)-N-(1-phenyl-1H-pyra-zol-5-yl)benzenesulfonamide (8): A solution of **6a** (0.01 mol) in formic acid (10 mL), was refluxed for 4 h. The solid obtained by filtration was crystallized from ethanol to give **8**. Yield: 70%; mp. 320-322°C; IR (KBr) ν (cm^{-1}): 3412, 3305 (2NH), 3097 (CH-arom.) 2925 (CH-aliph.), 1698, 1683 (C=O), 1169, 1233 (NH-SO_2). ^{1}HNMR: 1.33, 1.52 (2s, 6H, $2CH_3$), 2.11,2.31 (2s, 4H, $2CH_2$ cyclo), 4.5 (d, 5H, pyridine-H), 7,32(s,1H,CH-pyrimidine), 7.35-7.75 (m, 9H, Ar-H), 8.18-8.22 (d, 2H, pyrazole-H), 8.71 (s, H, NH), 8.87 (s, H, $NHSO_2$). MS: *m/z* (%) 619 (M^+, 0.6), 576 (0.8), 551 (0.11), 523 (0.11), 439 (0.17), 340 (0.47), 312 (100), 257 (52.23), 156 (4.21), 77 (5.18). Anal. Calcd. for $C_{33}H_{29}N_7O_4S$ (619); C, 63.96; H, 4.72; N, 15.82%. Found: C, 63.78; H, 4.47; N, 15.65 (**Scheme 2**).

N-(3-Cyano-7,7-dimethyl-5-oxo-1-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)-phenyl)-4-(pyridin-4-yl)-1,4,5,6,7,8-hexahydro-quinolin-2-yl)acetamide (9): A solution of **6a** (0.01 mol) in acetic anhydride (10 mL) was refluxed for 3 h. After cooling the solid obtained by filtration was crystallized from ethanol to give **9**. Yield: 76%; Mp. 220-222°C; IR: 3304, 3123 (NH), 3082 (CH-arom.), 2926 (CH-aliph.), 2229 (C=N), 1704, 1647 (C=O), 1156, 1232 ($NHSO_2$). ^{1}HNMR: δ 1.23, 1.93 (2s, 6H, $2CH_3$), 2.22, 2.41 (2s, 4H, $2CH_2$ cyclo), 2.51 (s, 3H, $COCH_3$), 4.1 (d, 5H, pyridine-H), 7.49-7.93 (m, 9H, Ar-H), 8.07, 8.11 (m, 2H, 2 pyrazole-H), 8.96 (s, 1H, NH), 11.11 (s, H, $NHSO_2$). MS: *m/z* (%) 633 (M^+, 0.28), 600 (0.26), 577 (0.43), 551 (0.74), 424 (0.38), 354 (19.11), 312 (100), 269 (1.1), 129 (7.12), 77 (91). Anal. Calcd. for $C_{34}H_{31}N_7O_4S$ (633): C, 64.44; H, 4.93; N, 15.47%. Found: C, 64.63; H, 5.12; N, 15.28 (**Scheme 3**).

N-Acetyl-N-(3-cyano-7,7-dimethyl-5-oxo-1-(4-(N-(1-phenyl-1H-pyrazol-5-yl)-sulfamoyl)phenyl)-4-(pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide(10): A solution of **6a** (0.01 mol) in acetic anhydride (10 mL) was refluxed for 24h. After cooling the solid obtained was crystallized from ethanol to give **10.** Yield: 60%; Mp. 300-302°C; IR (KBr)ν (cm^{-1}): 3122 (NH), 3088 (CH-arom.), 2973 (CH-aliph.), 2228 (C=N), 1704, 1728 (C=O). MS: *m/z (%)* 676 (M^+, 44.44), 543 (27.78), 439 (27.78), 300 (31.48),207 (31.48), 145 (35.19), 57 (100). Anal. Calcd. for



Scheme 3:

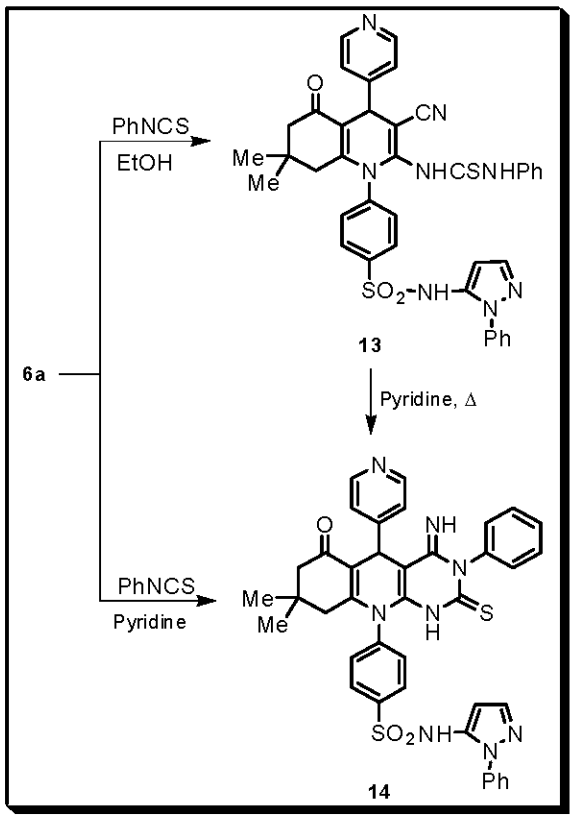


Scheme 4:

$C_{36}H_{33}N_7O_5S$ (675): C, 63.99; H, 4.92; N, 4.92%. Found: C, 64.05; H, 5.24; N, 4.71(**Scheme 3**).

4-(2-(2-Chlorophenyl)-8,8-dimethyl-4,6-dioxo-5-(pyridin-4-yl)-3,4,6,7,8,9-hexa-hydropyrimido[4,5-b]quinolin-10(5H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzene-sulfonamide (12): A mixture of **6a** (0.01 mole) and 2-chlorobenzoyl chloride (0.01 mole) in pyridine (20 mL) was refluxed for 12h. The obtained product was crystallized from dioxane to give **12**. Yield: 80%; mp. 320-322°C; IR: 3410, 3304 (NH), 3098 (CH-arom.), 2926 (CH-aliph.), 1648, 1590 (C=O). MS: *m/z (%)* 729 (13.58), 650 (16.05), 611 (13.58), 524 (17.28), 456 (17.28), 312 (35.80), 284 (24.69), 149 (30.86), 55 (100). Anal. Calcd. for $C_{39}H_{32}N_7O_4SCl$ (729.5): C, 64.15; H, 4.42; N, 13.43%. Found: C, 64.23; H, 4.67; N, 13.28(**Scheme 4**).

4-(3-cyano-7,7-dimethyl-5-oxo-2-(3-phenylthioureido)-4-(pyridin-4-yl)-5,6,7,8-tetrahydroquinolin-1(4H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (13): A mixture of **6a** (0.01 mole), phenyl isothiocyanate (0.01 mole) and absolute ethanol (30 mL) was refluxed for 5h. The solid obtained was crystallized from ethanol to give **13**. Yield: 80%; Mp. 320-322°C; IR: 3411, 3304 (NH), 3097 (CH-arom.), 2960 (CH-aliph.), 2221 (C=N), 1649 (C-O), 1117 (SO_2). ^{1}HNMR ($CDCl_3$): 1.13, 1.25 (2s, 6H, $2CH_3$), 1.96 (s, 4H, $2CH_2$-cyclo), 5.55 (s, 5H, pyridine-H), 7.26-7.66 (m, 14H, Ar-H), 8.11, 8.15 (d, 2H, 2CH pyrazole), 7, 93 (s, 2H, 2NH), 8.91 (s, 1H, $NHSO_2$). Anal. Calcd. for $C_{39}H_{34}N_8O_3S_2$ (726): C, 64.44; H, 4.71; N, 15.42%. Found: C, 64.53; H, 4.48; N, 15.64 (**Scheme 5**).



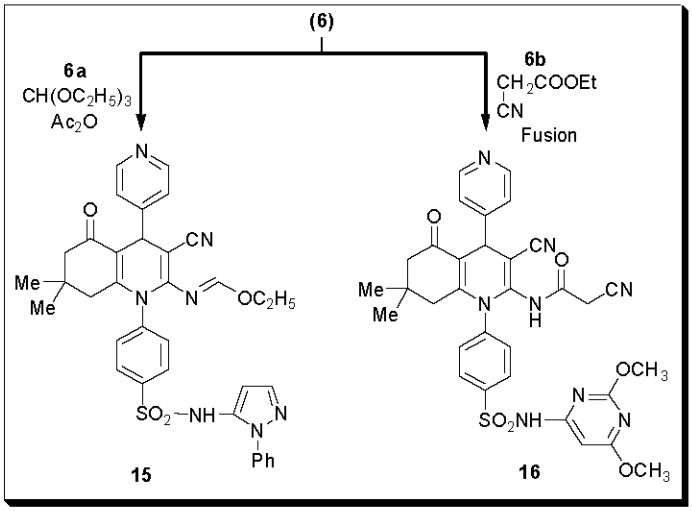
Scheme 5:

4-(4-Imino-8,8-dimethyl-6-oxo-3-phenyl-5-(pyridin-4-yl)-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10-5H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)-benzenesulfonamide (14):

Method (A): A mixture of **6a** (0.01 mol), phenyl isothiocyanate (0.01 mol) and pyridine (20 mL) was refluxed in an oil bath for 6h. The reaction mixture was cooled, diluted with ethanol and the resulting solid filter off was crystallized from dioxane to give **14**.

Method (B): A solution of **13** (0.01 mol) in pyridine (10mL) was refluxed for 5h. The reaction mixture was then cooled and diluted with aqueous ethanol to give **14**. Yield: 81%; Mp. 340-342°C; IR: 3408, 3300 (2NH), 3096 (CH-arom.), 1648 (C=O), 1589 (C=N), 1117, 1380 ($NHSO_2$). ^{1}HNMR: 1.07, 1.23 (2s, 6H, $2CH_3$), 2.51, 2.52 (2s, 4H, $2CH_2$-cyclo), 5.63 (m, 5H, pyridine-H), 7.61-7.81 (m, 14H, Ar-H), 7.93, 7.96 (2d, 2H, 2 pyrazole-H), 8.22, 8.26 (2s, 2H, 2NH), 8.89 (s, 1H, $NHSO_2$). MS: *m/z* (%) 727 (M^+, 3.52), 657(3.87), 565 (5.65), 551 (7.39), 389 (6.69), 354 (11.97), 261 (11.97), 171 (18.31), 77 (100). Anal. Calcd. for $C_{39}H_{34}N_8O_3S_2$ (726): C, 64.44; H, 4.71; N, 15.42%. Found: C, 64.30; H, 4.468; N, 15.68 (**Scheme 5**).

Ethyl-N-3-cyano-7,7-dimethyl-5-oxo-1-(4-(N-(1-phenyl-1H-pyrazol-5-yl)-sulfamoyl)phenyl)-4-(pyridin-4-yl)-1,4,5,6,7,8-hexa-hydroquinolin-2-yl- formimidate (15): A mixture of **6a** (0.01 mol), triethylorthoformate (2 mL) and acetic anhydride (10 mL) was refluxed for 8h. The reaction mixture was left to cool overnight and the solid formed was crystallized from ethanol to give **15**. Yield: 75%; Mp. 196-198°C; IR: 3122 (NH), 3031 (CH-arom.), 2924 (CH-aliph.), 2229 (C=N), 1704 (C=O), 1636 (C=N). MS: *m/z (%)* 648 (M^+, 4.2), 520 (0.56), 429 (0.66), 354 (81.71), 321 (3.61), 312 (100), 256 (6.07), 129 (6.81), 77 (14.89). Anal. Calcd. for $C_{35}H_{33}N_7O_4S$ (647): C, 64.90; H, 5.14; N, 15.14%. Found: C, 64.74; H, 4.93; N, 15.36 (**Scheme 6**).



Scheme 6:

2-Cyano-N-(3-cyano-1-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acet-amide (16): A mixture of compound **6b** (0.01 mol), ethylcyanoacetate (0.01 mol) and piperidine (0.5 mL) in dimethylformamide (10 mL) was heated under reflux for 3h. The solid product by filtration was collected by filtration and recrystallized from ethanol to give **16**. Yield: 70%; Mp. 120-122°C; IR: 3122 (NH), 3031 (CH-arom.), 2924 (CH-aliph.), 2229 (C=N), 1704 (C=O), 1636 (C=N). MS: *m/z* 654 (M^+, 0.42), 655 (M+1, 28), 420 (5.7), 377 (38.7), 222 (69.8), 155 (24.9), 91 (100). Anal. Calcd. for $C_{32}H_{30}N_8O_6S$ (654): C, 58.71; H, 4.62; N, 17.12%. Found: C, 58.47; H, 4.43; N, 17.43 (**Scheme 6**).

Antitumor Activity of the (E.A.C): The method used is that of trypan blue exclusion.

Reagents:

- RPMI 1640 medium (sigma).
- Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^6/mL).
- Trypan blue dye; A stock solution was prepared by dissolving one gram of the dye in distilled water (100 ml). The working solution was then prepared by diluting (1 mL) of the stock solution with (9 mL) of distilled water. The stain was used then for staining the dead EAC cells.
- The data of tested compounds are summarized in (Table 1).

Procedure: One mL of tumor cells which is drawn from mice bearing (E.A.C).

- EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions [23].
- In sterile test tubes, where 2.5×10^5 tumor cell/mL were suspended in phosphate buffer saline.
- Three different concentrations for each compound (25, 50, 100 µg/mL).
- Adding of 2.5×10^5 tumor cells for each tube.
- Incubation at 37°c for 2 hours.
- From sample cells + trypan blue [24, 25] volume by volume on slide.
- Examination under microscope.
- Dead cells stained blue and live cell not stained.
- Trypan blue exclusion test [26, 27] was carried out to calculate the percentage of non viable cells.
- Doxorubicin (Adriablastina) [28] is taken as a reference.

Table 1: *In vitro* antitumor activity of some newly synthesized compounds.

	Non-viable cells (%)		
	Concentration (µg/mL)		
Compd. No.	100	50	25
6a	95	80	60
6b	95	70	50
7	50	20	10
8	40	10	0
10	30	0	10
13	85	50	40
14	30	0	0
15	90	60	40
Doxorubicin	100	55	20

$$\% \text{ of non-viable cells} = \frac{\text{No. of non viable}}{\text{Total No. of cells}} \times 100$$

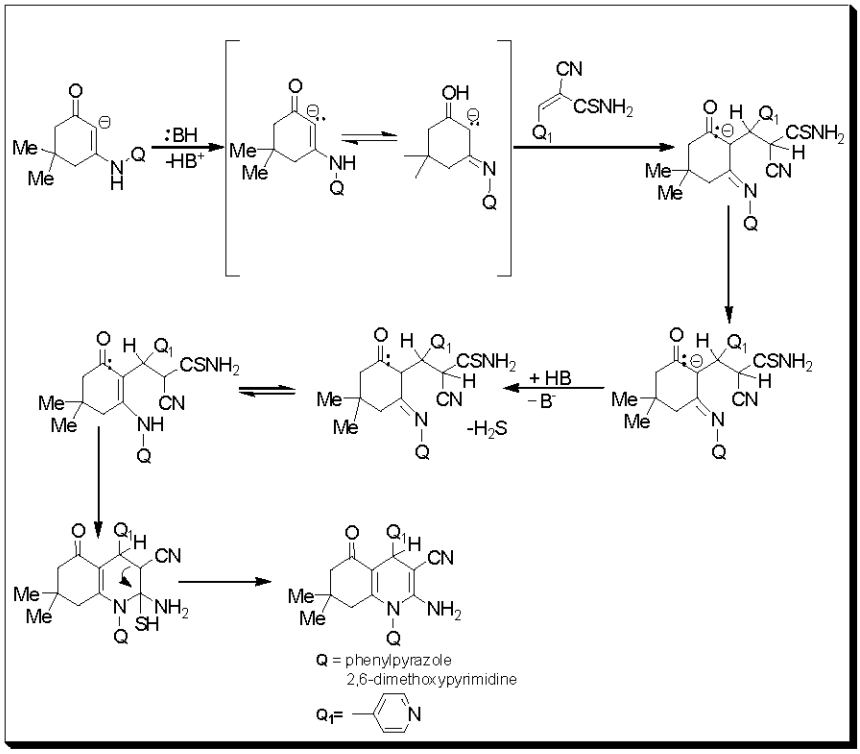
The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of EAC cell. The response parameter calculated was IC50 value which corresponds to the compound concentration causing 50% mortality in net cells (Table 1). The results obtained from this study showed that pyrazole having quinoline containing free cyano with amino group and sulfonamide moieties (6a-b) and pyrazole having thiourea, formimido and sulfonamide moieties [10,12] is more effective than the positive control (Doxorubicin) with IC50, respectively. Also, pyrazole having pyrimidine, thiopyrimidine and sulfonamide moieties [4, 5, 10] is nearly as active as the positive control Doxorubicin with IC50 of 50 g/ml, respectively.

RESULTS AND DISCUSSION

Enaminone **3** was obtained from condensation of 5, 5-dimethylcyclohexan1, 3-dione **1** with sulfaphenazole or sulfadimethoxine **2a, b**. It was reported [29-32] treatment of enaminone of type **3** with 4-arylidenethiocyanoacetamide **4** and in presence of piperidine as a catalytic base leads to the formation of the hexahydroquinoline derivatives of the type 6a,b and this cyclo addition reaction takes place via 1,2-like *Michael addition.*

In this paper, treatment of the new enaminones 3a&3b with 4-pyridinylidene thiocyanoacetamide **4** [33] under the above mentioned conditions led to the formation of the tetrahydroquinoline derivatives 6a and 6b, respectively (**Scheme 1**).

Scheme 1: *N*-Heteroaryl substituent decreases the nucleophilicity of the enaminoketone **3** toward 2-cyano-2-(pyridin-4-yl)thiocyanoacetamide **4**, a base catalyst was required to achieve the formation of hexahydroquinolines **6a,b** [30-32]. Presumably, the base generates the anion of the 3-aminocyclohex-2-en-1-one **3**, thus facilitating the addition to the unsaturated nitrile **4**. The formation of compounds 6a, b can be rationalized via the following mechanism.



The behavior of compound **6a** towards acid derivatives was also investigated. Thus, pyrimidopyrazoloquinoline derivative **7** was obtained by cyclocondensation of compound **6a** with formamide [34]. Refluxing of compound **6a** with excess formic acid caused cyclization and gave the corresponding pyrimidoquinoline derivative **8**, [35, 36] (**Scheme 2**). The formation of **8** is supposed to proceed *via* intermediate amide formation, resulted from the hydrolysis of cyano functionality present at the position 3 of **6a**, followed by intermolecular cyclization with formic acid and loss of two molecules of water (**14**).

Scheme 2: The reaction of compound **6a** with acetic anhydride led to the formation of the diacetyl derivative 10 and not the mono acetyl [24],based upon the special and micro analytical data (**Scheme 3**).

Scheme 3: The hydrolysis of the cyano group into the amido group must be achieved firstly. Interaction of compound **6a** with 2-chlorobenzoyl chloride afforded the pyrimidopyrazoloquinoline drivative **12** [25] (**Scheme 4**).

Scheme 4: In addition, the behavior of compound **6a** towards phenyl isothiocyanate under different conditions was also studied. Thus, the reaction of compound 6a with phenyl isothiocyanate in boiling ethanol afforded a product for which two structures **13** and **14** seemed possible. Structure **13** was established for the reaction product on the basis of its IR spectrum, which showed the presence of (C≡N) band. Compound 6a reacted with phenyl isothiocyanate in pyridine to give pyrimidopyrazoloquinoline derivative **14**. Compound 13 was obtained via the reaction of 6a with phenylisothiocyanate in absolute ethanol which when refluxed in pyridine yielded compound 14., Compound 14 which obtained by the tow pathways show on depression in admixed m.p. (**Scheme 5**).

Scheme 5: The enaminonitrile **6a** reacted with triethylorthoformate in acetic anhydride and yielded the ethoxymethylideneamino derivative **15**. By using triethylorthoformate only the same product **15** was obtained in good yield. This work was extended to cover the reactivity of compound **6b** toward activated nitrile

compounds. Thus, condensation of compound **6b** with ethyl cyanoacetate under condition of fusion gave a product which was formulated as hydroquinoline derivative **16** based upon the special and micro analytical data (**Scheme 6**).

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