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Synthesis and Antimicrobial Evaluation of Some New Pyrozolo, Triazolo[1,5-*a*] Pyrimidines and Pyrido, Pyrimido [1,2-*a*] Benzimidazole Based Heterocycles

Amani A.Elrazig, Salman A. Aziz*[1]and Ahmad M. Farag[2]

*1-Department of Chemistry, Faculty of Science, Sudan University, Khartoum, Sudan. E-mail: amani.salman.2@gmail.com
2-Department of Chemistry, Faculty of Science, Cairo University, Giza 12622, Egypt.
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ABSTRACT

A simple, facile, procedure for the synthesis of pyrazolo[1,5-a]pyrimidines, triazolo[1,5-a] pyrimidines and primido[1,2-a]benzimidazoles ring systems incorporating a phenylsulfonylbenzothiazole moiety was developed via the reaction of 1-(benzothiazol-2-yl)-3-*N*,*N*-(dimethylamino)-2-(phenylsulphonyl)prop-2-en-1-one with substituted 4-arylazo-3,5-diaminopyrazoles, 3-amino-1,2,4-triazole, 2-aminobenzimidazole, 1*H*-benzimidazol-2-ylacetonitrile and 5-amino-1*H*-pyrazole derivatives. Antimicrobial and antifungal activities of some new products were evaluated.

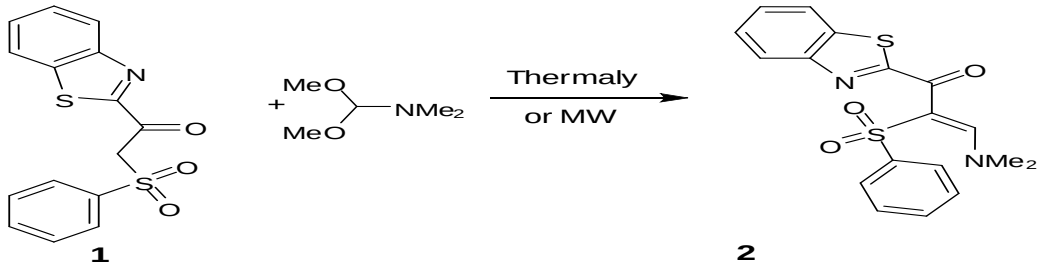
المستخلص

الطرق البسيطة لتحضير بايدزول بريميدينات ، ترايزول بريميدينات و بايريدو بنزواميدزول التي تشتمل على فينيل سفونيل بنزوثيازول،حيث نتحصل عليها عن طريق تفاعل بنزاميدزيل – ن–ن – ثنائي ميثل امينو –2– فنيل بروبينون مع مشتقات –4– أريل أزو–5،3– ثنائي امينو بايرزول ، 3–امينو – 4،2،1–ترايزول ، 2–امينو بنزواميدزول ،1–بنزاميدزول –2– أسيتونيتريل و مشتقات 5– امينو 1–بايرزول .أيضا تم تقييم فعالية بعض المنتجات الجديدة ضد بعض الميكروبات والفطريات .

***KEYWORDS*:** Pyrazolo[1,5-a]pyrimidines; pyrimido[1,2-a]benzimidazoles**;** 5-amino-1H-pyrazole

INTRODUCTION

Benzothiazoles are one of sulfur and nitrogen-containing aromatic heterocyclic compounds, which are formed from fusion of the aryl and thiazolyl rings. They have diverse interesting medical and industrial applications[(1)]. Many studies on the synthesis and anti-tumor activity of benzothiazole derivatives displayed a potent and a selective anti-tumor activity against different types of tumors such as breast, ovarian, lung, renal cell lines, and colon cancer. Moreover, those studies also demonstrated that benzothiazole derivateives have antimicrobial, antitubercular, anti-inflammatory, antirheumatic and antiglutamate activities[(2-10)]. Enaminones constitute an interesting class of compounds that are versatile for the synthesis of a great variety of heterocyclic and aromatic compounds [(11-14)]. Their structural features constitutes many compounds of anticonvulsive [(15)] and anti-histaminergic activities[(16)].



Conventional method : 8h, EtOH92-94% conversion yield
Microwave method : 20 min,EtOH,83-88% conversion yield

Scheme 1

The reactivity of the enaminosulphone 2, in general, can be attributed to the fact that their molecules have two electron centers at C-1 and C-3 a long with one electron rich center at C-2 which is due to the delocalization of the lone pair of electrons on the nitrogen atom in addition to conjugation with the sulfone group as shown in (Figure 1).

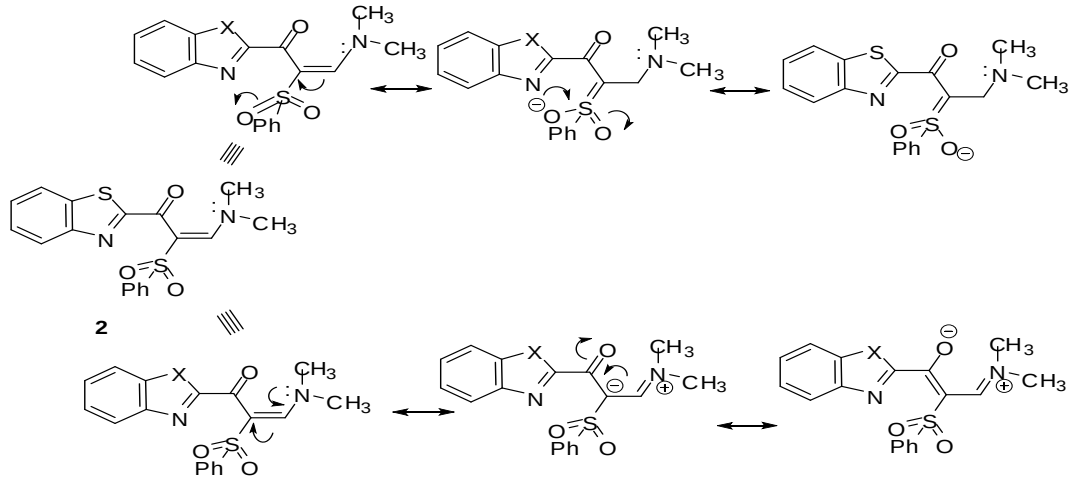


Figure 1:

MATERIALS and METHODS

Melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in deuterated dimethylsulfoxide [D6] DMSO. Mass spectra were measured on a Varian MAT CH-5 spectrometer (70 eV).5-amino-1*H*-pyrazole derivatives 3a,b and 4d[17], 4-arylazo-3,5-diaminopyrazoles 8a,b[18],were prepared according to the reported literature. In the present study, the starting compound enaminone 2 was readily obtained by the reaction of equimolar quantities of 1-(benzothiazothiazol-2-yl)-2-phenylsulfonyl-1-ethanone(1) with dimethylformamide-dimethylacetal (DMF-DMA) in toluene under reflux and under microwave condition (scheme 1). The structure of 1-(benzothiazol-2-yl)-3-*N*, *N*-(dimethylamino)- 2- (phenyl sulphonyl)prop-2-en-1-one (2) was confirmed by their elemental analyses

and spectral data. For example, the ^1H NMR spectrum of 2 displayed a singlet signal at δ 3.05 due to *N*,*N*-dimethyl protons, singlet at δ 7.87 due to olefinic proton, in addition to an aromatic protons multiplet in the region δ 7.35-8.03.

Reaction ofenaminone 2with 5-amino-3-aryl-4-substituted pyrazole 3a-c, 4d and 8a,b

(A)-Thermal method:

General procedure:

To a mixture of the enaminone 2 (3.72 g, 10 mmol) and the appropriate aminopyrazole derivative (10 mmol), in absolute ethanol (25 ml), few drops of piperidine was added and the reaction mixture was refluxed for 6 hrs. The solid product was filtered off, washed with ethanol and recrystallized from ethanol/DMF to afford the pyrazolo[1,5-*a*]pyrimidine derivatives 7a-d and 10a,b.

(B)-Microwave method (MW):

General procedure:

To a mixture of the enaminone 2 (0.372 g, 1mmol) and the appropriate aminopyrazole derivatives (1 mmol), in absolute ethanol (2.5 ml), few drops of piperidine were mixed in a process vial. The vial capped properly and irradiated with microwave under conditions (17.2 bars, 130 ^oC) for 20 min. The solid product was filtered off, washed with ethanol and recrystallized from ethanol/*DMF* to afford the pyrazolo 1,5-*a*]pyrimidine derivatives 7a, and 10a.

The physical and spectral data of the synthesized compounds 7a-d, and 10a,b (thermal and MW) are listed below

2-(2-phenyl-6-(phenylsulfonyl)pyrozolo(1,5-*a*)pyrimidin-7-yl)benzothiazole (7a)

Yield 71% (thermally), 89% (MW); mp. 228-230˚C. IR (KBr) υ_{max} /cm^{-1}: 1596 (C=N). ^{1}H NMR (DMSO-d_6): δ7.07 (s, 1H, pyrazole-3-CH), 7.44-8.38 (m, 14H, ArH's), 9.25(s, pyrimidine-5-CH).^{13}C NMR (DMSO-d_6): 93.31, 121.52, 121.78, 124.32, 125.98, 127.32, 128.53, 128.13, 129.48, 129.12, 131.31, 133.08, 133.21, 133.94, 141.54, 148.05, 153.65, 154.72, 156.31, 155.31, 162.81. MS (*m/z*): 468 (M$^+$, 100%), 77 (36.2%). Anal. Calcd for $C_{25}H_{16}N_4O_2S_2$: C, 64.08; H, 3.44, S, 13.69; N, 11.96%. Found: C, 63.92; H, 3.52, S, 13.57; N, 11.66%.

2-(2-(4-Chlorophenyl-6-(phenylsulfonyl)pyrozolo(1,5-*a*)pyrimidin-7-yl)benzothiazole(7b)

Yield 75%; mp. 224-226˚C. IR (KBr) υ_{max} /cm^{-1}: 1596 (C=N). ^{1}H NMR (DMSO-d_6): δ 6.71 (s, 1H, pyrazole-3-CH), 7.45-8.17 (m, 13H, ArH's), 9.22(s, pyrimidine-5-CH). MS (*m/z*): 502 (M$^+$, 100%), 77 (36.2%). Anal. Calcd for $C_{25}H_{15}N_4ClO_2S_2$: C, 59.70; H, 3.01, S, 12.75; N, 11.14%. Found: C, 59.62; H, 3.12, S, 12.69; N, 11.10%.

2-(6-phenylsulfonyl)-2-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidin-7-yl)benzothiazole(7c)

Yield 75%; mp. 190˚C. IR (KBr) υ_{max} /cm^{-1}: 1594 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.31(s, 3H, CH_3), 6.69 (s, 1H, pyrazole-3-CH), 7.29-8.20 (m, 13H, ArH's), 9.24 (s, pyrimidine-5-CH). MS (*m/z*): 482 (M$^+$, 100%). Anal. Calcd for $C_{26}H_{18}N_4O_2S_2$: C, 64.71; H, 3.76, S, 13.29; N, 11.61%. Found: C, 64.68; H, 3.72, S, 13.31; N, 11.66%.

7-(-benzothiazol-2-yl)-6-(phenylsulfonyl)pyrozolo(1,5-*a*)pyrimidine-3-carbonitrile (7d)

Yield 73%; mp. 128-129˚C. IR (KBr) υ_{max} /cm^{-1}: 1596 (C=N),2194 (C≡N). ^{1}H NMR (DMSO-d_6): δ 8.77 (s, 1H, pyrazole-2-CH), 7.43-8.20 (m, 9H, ArH's), 9.25 (s, pyrimidine-5-CH). MS (*m/z*): 417 (M$^+$, 100%), 77 (36.2%). Anal. Calcd for $C_{20}H_{11}N_5O_2S_2$: C,

57.54; H, 2.66, S, 15.36; N, 16.78%. Found: C, 57.52; H, 2.59, S, 15.37; N, 16.79%.

7-(Benzothiazol-2-yl-3-phenyldiazenyl)-6-(phenylsulfonyl)pyra-zolo[1,5-*a*]pyrimidine-2-amine (10a)

Yield 66% (thermally), 86%(MW); mp. 270-269˚C. IR (KBr) υ_{max} /cm^{-1}: 3398, 3277 (NH_2), 1588 (C=N). ^{1}H NMR (DMSO-d_6): δ 6.48 (s, 2H, NH_2, D_2O exchangeable), 7.44-8.22 (m, 14H, ArH's), 9.23 (s, pyrimidine-5-CH). MS (*m/z*): 511 (M^+, 100%), 77 (46.1%). Anal. Calcd for $C_{25}H_{17}N_7O_2S_2$: C, 58.69;; H, 3.35, S,12.54; N, 19.17%. Found: C, 58.41; H, 3.28, S, 12.42; N, 19.22%.

7-(Benzthiazol-2-yl)--3-(*p*-tolyldiazenyl)-6-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-2-amine (10b)

Yield 68%; mp. 224-226˚C. IR (KBr) υ_{max} /cm^{-1}: 3408, 3297 (NH_2), 1588 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.30(s, 3H, CH_3), 6.68. s, 2H, NH_2, D_2O exchangeable), 7.43-8.20(m, 14H, ArH's), 9.25 (s, pyrimidine-5-CH). MS (*m/z*): 525 (M^+, 100%), 77 (16.1%). Anal. Calcd for $C_{26}H_{19}N_7O_2S_2$: C, 59.41; H, 3.64, S, 12.20; N, 18.65%. Found: C, 59.39; H, 3.62, S, 12.23; N, 18.67%.

Reaction of enaminone 2 with 3-amino-1,2,4-triazole (11), 2-amino-benzimidazole (14) and 2-cyanomethylbenzimidazole (17)

(A)-Thermal method:

General procedure:

To a mixture of enaminone 2(3.72 g, 10 mmol)and the appropriate heterocyclic amines (3-amino-l,2,4-triazole (11), 2-aminobenzimidazole (14) or 2-cyano-methylbenzimidazole (17)**)** (10mmol) in pyridine (25 ml) was refluxed for 12 h, and left to cool. The solvent was evaporated in *vacuo* and the residual solid was taken in ethanol and collected by filtration, washed with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding triazolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole or pyrido[1,2-*a*] benzimidazole derivatives 13**,** 16 and19 respectively..

(B)-Microwave method (MW):

General procedure:

To a mixture of enaminone 2(0.372 g, 1 mmol)and the appropriate heterocyclic amines (3-amino-l,2,4-triazole (11) and 2-aminobenzimidazole (14)) (1mmol) in pyridine (2.5 ml) were mixed in a process vial. The vial capped properly and irradiated with microwave under conditions (17.2 bars, 130 ^{o}C) for 20 min. The solvent was evaporated in *vacuo* and the residual solid was taken in ethanol, collected by filtration, washed with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding triazolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole or pyrido[1,2-*a*]benzimidazole derivatives 13 and16respectively.

The physical and spectral data of the synthesized compounds (thermal & MW) 13, 16,and19 are listed below.

2-(6-(Phenylsulfonyl)-[1,2,4]-triazolo[1,5-*a*]pyrimidin-7-yl)benzothiazole (13)

Yield 63% (Thermally), 88%(MW); mp. 155˚C. IR (KBr) υ_{max} /cm^{-1}: 1611 (C=N). ^{1}H NMR (DMSO-d6): δ 7.21-8.13 (m, 9H, ArH's), 8.60 (s, 1H,triazole-2-CH), 9.11(s, pyrimidine-5-CH). MS (*m/z*): 393 (M^+, 100%), 77 (31.5.1%). Anal. Calcd for $C_{18}H_{11}N_5O_2S_2$: C, 54.95; H, 2.82, S, 16.30; N, 17.80%. Found: C, 54.89; H, 2.86, S, 16.26; N, 17.83%.

3-(Benzothiazol-2-yl)(2-(phenylsulfonyl)pyrimido[1,2-*a*]benzimidazole (16)

Yield 73%(Thermally), 92%(MW); mp. 262-263 ˚C. IR (KBr) υ_{max} /cm^{-1}: 1620 (C=N).

^{1}H NMR (DMSO-d6): δ 7.57-8.75 (m, 13H, ArH's), 9.21 (s, pyrimidine- 1-CH). ^{13}C NMR (DMSO-d_6): δ 114.33, 118.72, 119.79, 120.60, 122.59, 123.52, 123.78, 126.93, 127.23, 127.37, 127.82, 128.64, 132.98, 135.55, 142.53, 143.74, 145.51, 151.11, 152.93, 163.95. MS (*m/z*): 442 (M^+, 100%), 77 (12.9%). Anal. Calcd for $C_{23}H_{14}N_4O_2S_2$: C, 62.43;; H, 3.19, S, 14.49; N, 12.66%. Found: C, 62.41; H, 3.25, S, 14.52; N, 12.59%.

3-(Benzothiazol-2-yl)(2-(phenylsulfonyl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (19).

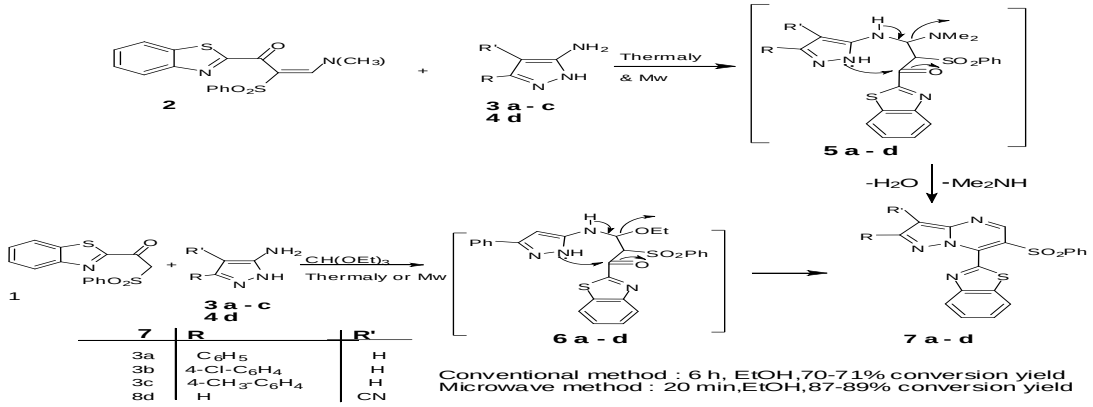
Yield 75%; mp. 214 ˚C. IR (KBr) υ_{max} /cm^{-1}: 2233 (C≡N), 1598 (C=N). ^{1}H NMR (DMSO-d6): δ 7.48-8.53 (m, 13H, ArH's), 9.23 (s, 1H,pyridine-1-CH). MS (*m/z*): 466 (M^+, 80.3%), 263 (100%), 161 (10.5%), 77(13.6%). Anal. Calcd for $C_{25}H_{14}N_4O_2S_2$: C, 64.36; H, 3.02, S, 13.75; N, 12.01%. Found: C, 64.37; H, 3.05, S, 13.69; N, 12.03%.

RESULTS and DISCUSSION

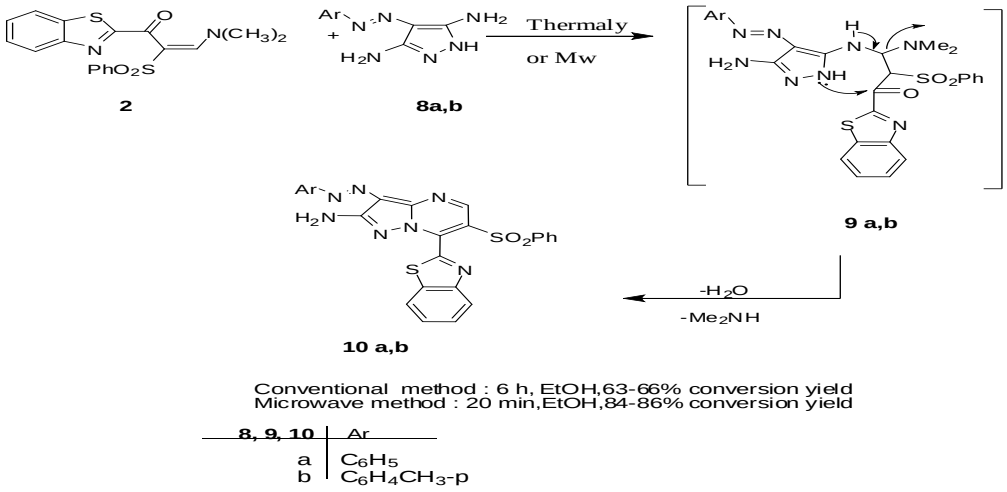
The behavior of the enaminone 2 towards some nitrogen nucleophiles such as aminopyrazole derivatives as potential precursors for the synthesis of interesting biologically active pyrazolo[1,5-*a*]pyrimidines[19] was also investigated. Thus, when the enaminone 2 was treated with substituted 5-amino-1*H*-pyrazole derivatives 3a,b and 4, in ethanol in the presence of catalytic amount of piperidine under reflux and microwave conditions, they afforded the corresponding pyrozolo[1,5-*a*]pyrimidine derivatives 7a-d in almost quantitative yield (Figuer 2).

The structure of compound 7a-d was established on the basis of their elemental analyses and spectral data. For example, the mass spectrum of compound 7a, revealed a molecular ion peak at *m/z* 468. ^{1}*H* NMR spectrum revealed a singlet signal at δ 9.25 due to pyrimidine proton (CH-5) in addition to aromatic protons as a multiplet at δ 7.44-8.38.

The IR spectrum of the same compound showed no peak due to carbonyl absorption. The IR spectrum of compounds 7d revealed a band near 2194 cm^{-1}due to CN absorption (see Experimental part).Moreover, the structures of compounds 7a-d was further supported by independent synthesis from the reaction of 1-(benzothiazothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (1) with the heterocyclic amines 3a,b and 4 and triethyl orthoformate, in the presence of a catalytic amount of piperidine in one pot reaction, which afforded products 7a-d identical in all respects (m.p., mixed m.p. and IR spectra) with those obtained from the reaction of the enaminone 2 with 5-amino-1*H*-pyrazole derivatives (Scheme 2).

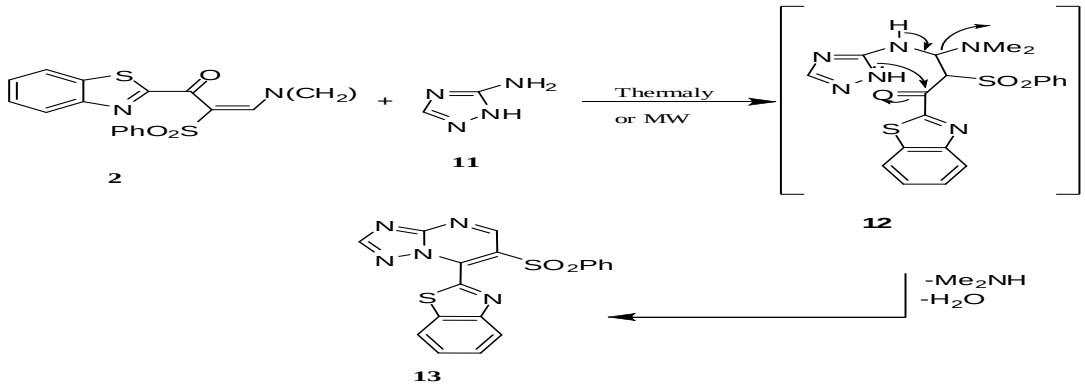


Similarly, the enaminone 2 react with 4-arylazo-3,5-diaminopyrazoles 8a,b under the same experimental conditions, to afford the corresponding polysubstituted pyrazolo[1,5-*a*] pyrimidines 10a,b (Figure 3). The structure of product 10a,b was established on the basis of their elemental analyses and spectral data.



Figuer 3:

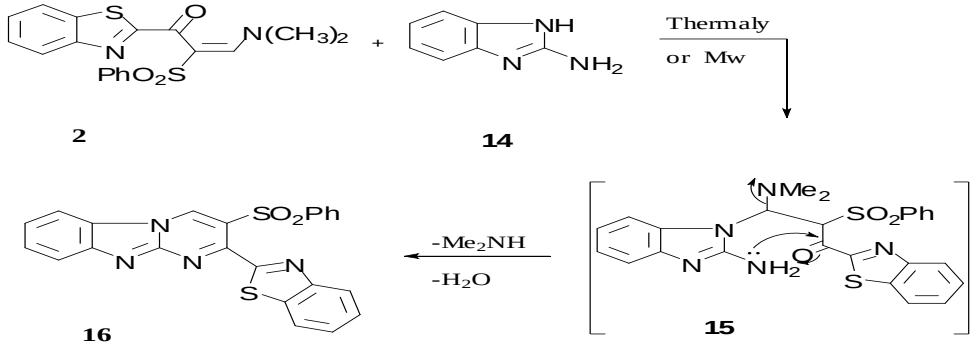
The enaminone **2** react also with 3-amino-1,2,4-triazole (11), in refluxing pyridine, to afford 2-(6-phenylsulfonyl-[1,2,4]-triazolo[1,5-*a*]pyrimidin-7-yl)benzothiazole (13) (Figuer 4). The ^{1}H NMR spectrum of 13 revealed a singlet signal at δ 9.11 due to pyrimidine proton (CH-5) in addition to aromatic protons as a multiplet signals at region at δ 7.21-8.13. The IR spectrums of the same compound revealed the absence of any band due to carbonyl absorption.A plausible mechanism for the formation of compound 13 is outlined in (Scheme 4). Compound 13 was assumed to be formed *via* an initial Michael-type addition of the amino group of 3-amino-1,2,4-triazole (11) to the activated double bond in the enaminone 2 and followed by elimination of dimethylamine and water molecule from the non-isolable intermediate 12 to afford the final product13 (Figure 4**)**.



Conventional method :12 h, pyridine, 62-63% conversion yield
Microwave method : 20 min, pyridine, 86-88% conversion yield

Figuer 4

In contrast to its behavior towards 3a,b, 8a,b and 11, the enaminone 2 reacted with 2-aminobenzimidazole (14) in refluxing pyridine and microwave conditions to afford only one isolable product (as examined by TLC) The reaction product was identified as 3-(benzothiazol-2-yl)(2-(phenylsulfonyl)pyrimido[1,2-*a*]benzimidazole (16) (Figuer 5). The spectral data of the isolated products 16 was in complete agreement with the assigned structures. For example, the IR spectra of 16 revealed no bands due to amino or carbonyl functions. Moreover, their ^{1}H NMR spectra revealed an aromatic multiplet in the region δ 7.45-8.75 and a singlet signal at δ 9.21 due to pyrimidine proton.The formation of compounds 16 was assumed to take place *via* an initial Michael-type addition of the imino function (endocyclic nitrogen)[20,21] in compound 14 to the double bond in the enaminone 2 to give the acyclic non-isolable intermediates 15, which undergo intramolecular cyclization *via* the loss of dimethylamine and water molecules to afford the final isolable products 16 (Figuer 5).

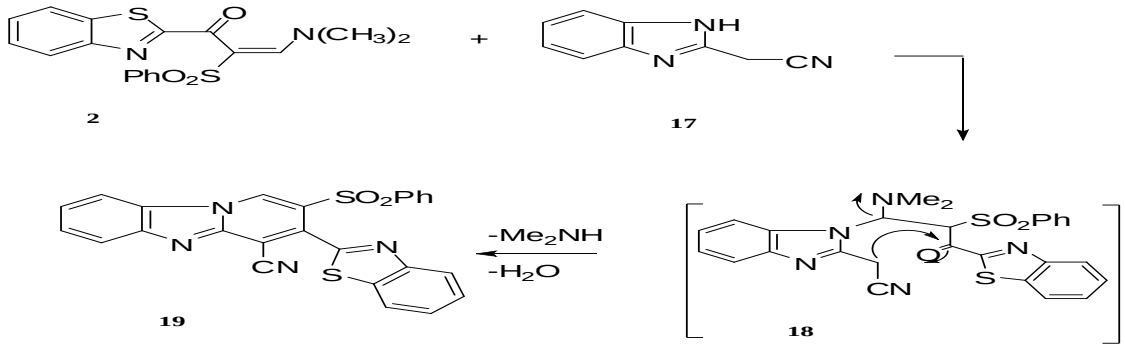


Conventional method :12 h, pyridine, 70-73% conversion yield
Microwave method : 20 min, pyridine, 91-92% conversion yield

Figuer 5:

In a similar manner, the enaminone 2 react with 1*H*-benzimidazol-2-ylacetonitrile (17) in refluxing pyridine and microwave condition to afford only one isolable product (as examined by TLC). The reaction product was

identified as 3-(benzothiazol-2-yl)(2-(phenylsulfonyl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (19) (Figuer 6). The structure of compounds 19 was assigned on the basis of their elemental analyses and spectral data. For example, the IR spectrum showed a characteristic absorption band at 2233 cm^{-1} due to cyano group and revealed the absence of absorption bands corresponding to carbonyl groups.



Figuer 6:

Biological Evaluation

Using the diffusion plate method, [22-23] a bottomless cylinder containing a measured quantity (1mL, 0.1mg/ml) of the sample was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which has been heavily seeded with the spore suspension of the test organism. After incubation (24 h for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as measure of the inhibitory power of the sample against the particular test organism. The test results are depicted in Table 1.

Table 1: Antimicrobial Activity of the Tested Compounds

COMPOUNDS NO.	INHIBITION ZONE DIAMETER (IZD) (MM/MG COMPOUND TESTED) Gram (+)		Gram (-)		Fungi & Yeast	
	(SA)*Staphylococcus aurous* **anaerobic**	**(BS)** *Bacillus subtilis*	**(EC)***Escherichia coli*	**(ST)** *Salmonella typhimurium*	**(AF)** *Aspergillus fumigatus*	**(CA)***Candida albicans*
CONTROL	0.0	0.0	0.0	0.0	0.0	0.0
7a	16	20	15	16	12	13
7b	22	15	18	11	13	9
7c	21	15	17	10	12	10
7d	19	14	17	15	13	10
10a	11	9	10	11	6	5
10b	20	14	16	11	19	11
13	23	20	21	18	20	11
16	20	16	13	15	12	13
19	16	13	15	12	15	10
Control #	**35**	**35**	**36**	**38**	**35**	**37**

Activity index:

The activity of tested compounds were categorized as follows:

- The solvent used was ethanol.
- Concentration of the sample in 100 µg/ml.
- IZD = 2-10 mm beyond control = + (low activity).
- IZD = 11-24 mm beyond control = ++ (Moderate activity).
- IZD = 25-35 mm beyond control = +++ (high activity).
- #: Chloramphencol in the case of Gram - positive bacteria, Cephalothinin the case of Gram – negative bacteria and cycloheximide in the case of fungi.

The selected compounds were tested against gram negative bacteria; Escherichia coli (EC) and *Salmonella typhimurium*, gram positive bacteria; Staphylococcus aurous (SA) and *Bacillus subtilis* , antifungal activity against, *Aspergillus fumigatus* and Yeast; Candida albicans (CA). Cephalothin and cycloheximide were used as references antibiotics to evaluate the potency of the tested compounds under the same condition.

The test results revealed that all compounds exhibited moderate activity against two bacterial species, *Aspergillus fumigatus* and Candida albicans (CA).

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