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RESEARCH ARTICLE

Synthesis of Potent Antimicrobial Pyrrole Derivatives

Maher A. El-Hashash[1], Sherif M. Sherif [2], Azza A. E. Badawy[1], Huda R. M. Rashdan[3*]

1. Department of Chemistry, Faculty of Science, Ain-Shams University, Cairo, Egypt.

2. Department of Chemistry, Faculty of Science, Cairo University, Giza12613, Egypt (Dean of Faculty of Science, Cairo University).

3. Department of Chemistry of Natural and Microbial Products, Pharmaceutical and Drug Industries Research Division, National Research Center, Giza, Egypt.

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Corresponding Author

Huda R. M. Rashdan

Abstract

Several new pyrrole derivatves were synthesized *via* the reaction of 2,5-dihydro-4,5-bis(4-methoxyphenyl)-2-Thioxo-1*H*-pyrrole-3-carbonitrile with ethyl chloroacetate, chloroacetone, ω-bromoacetophenone, ω-bromo-4-methylacetophenone, chloroacetonitrile or iodomethane to give the corresponding s-alkylated derivatives. In addition, the antimicrobial activity of some selected derivatives was studied.

INTRODUCTION

Pyrroles have received enormous attention from synthetic chemists from the stand point of both their preparation and their reactivity. The pyrrole nucleus is the characteristic structural motif of numerous natural and synthetic products for example (storniamide A, lamellarin P, marinopyrrole B) (fig. 1) [1]. Many poly functionalized pyrrole derivatives are known to display interesting biological activities, as antilipidemics [2], antioxidants [3] and anti-inflammatories [4,5]. They are also antibacterials [6,7], antitumorals [8], as well as anti-fungal [9], antitubercular [10], and central nervous system agents [11]. In addition, pyrroles were observed to inhibit cytokine-mediated diseases [12] and have also found some applications materials chemistry [13]. The growing importance and wide applications of poly substituted pyrrole derivatives have kept in focus the search of new methods for the facial synthesis of these ring systems. Pyrroles have been prepared *via* several classical methods [14] such as Barton-Zard [15], Hantzsch [16,17], Knorr [18,19], Trofimov [20], Pall-Knorr [21,22] and Clasuon-Kass [23] reactions and their modifications.

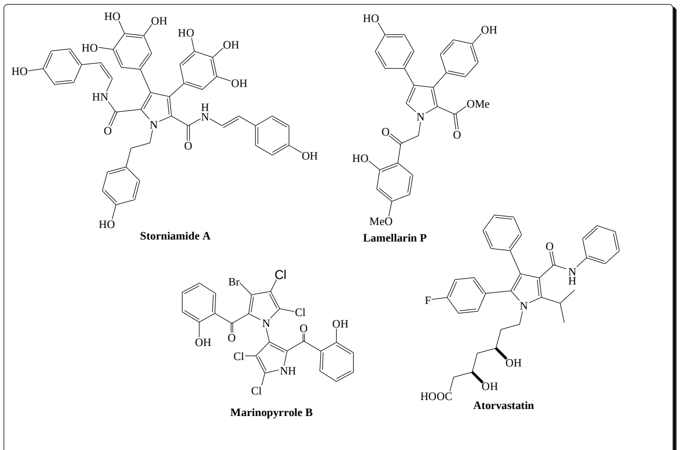
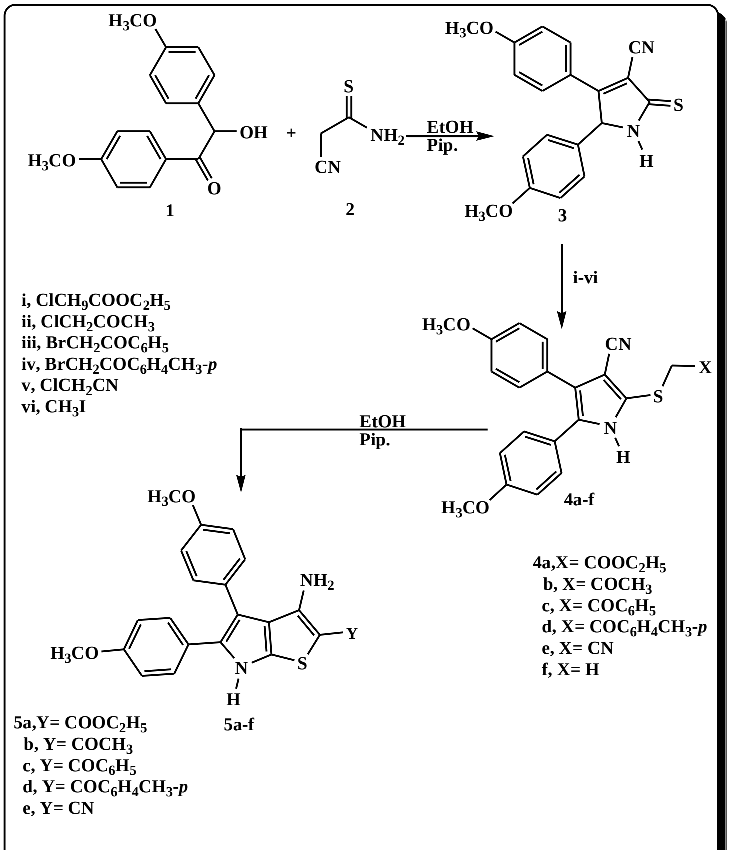


Fig 1.Examples of natural(Storniamide A, Lamellarin P, Marinopyrrole B) and synthetic(Atorvastatin) polysubstituted pyrroles.

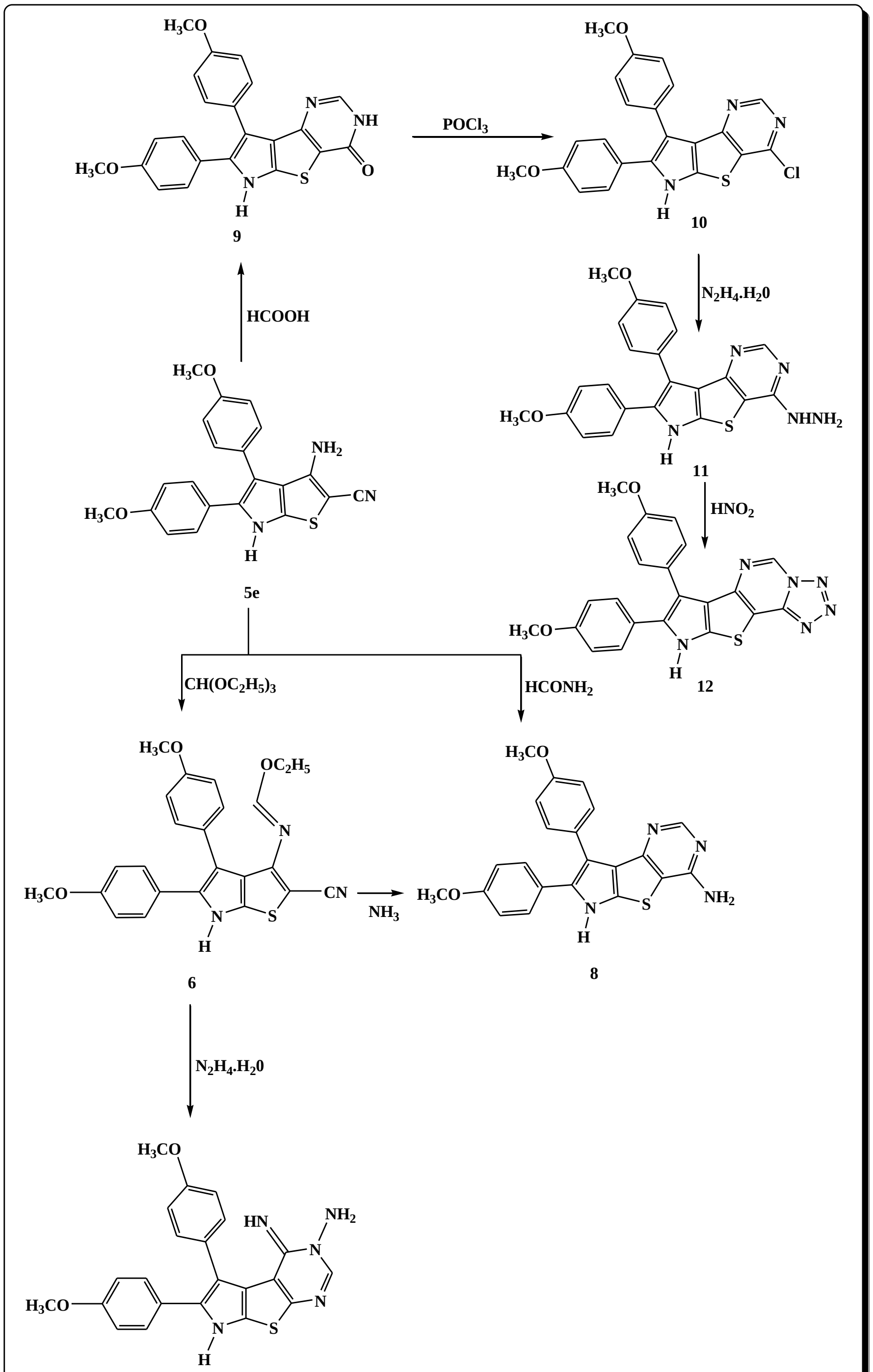
1. Result and discussion

It has been found that anisoin **1** reacted with cyanothioacetamide **2** in absolute ethanol containing catalytic amount of pipredine to afford 2,5-dihydro-4,5-bis(4-methoxyphenyl)-2-thioxo-1*H*-pyrrole-3-carbonitrile (**3**) in a good yield. The latter reacted with each of ethyl chloroacetate, chloroacetone, ω-bromoacetophenone, ω-bromo-4-methylacetophenone, chloroacetonitrile or iodomethane to give the corresponding s-alkylated derivatives **4a-f**, respectively. Structures **4a-f** were elucidated by elemental analysis, spectral data (IR, H^1NMR, Mass) and chemical transformation. Thus, boiling of pyrrole derivatives **4a-e** in ethanol in presence of catalytic amount of piperidine afforded the corresponding 4,5-bis(4-methoxyphenyl)-2-substituted-6*H*-thieno[2,3-*b*]pyrrol-3-amine (**5a-e**), respectively (Scheme1).



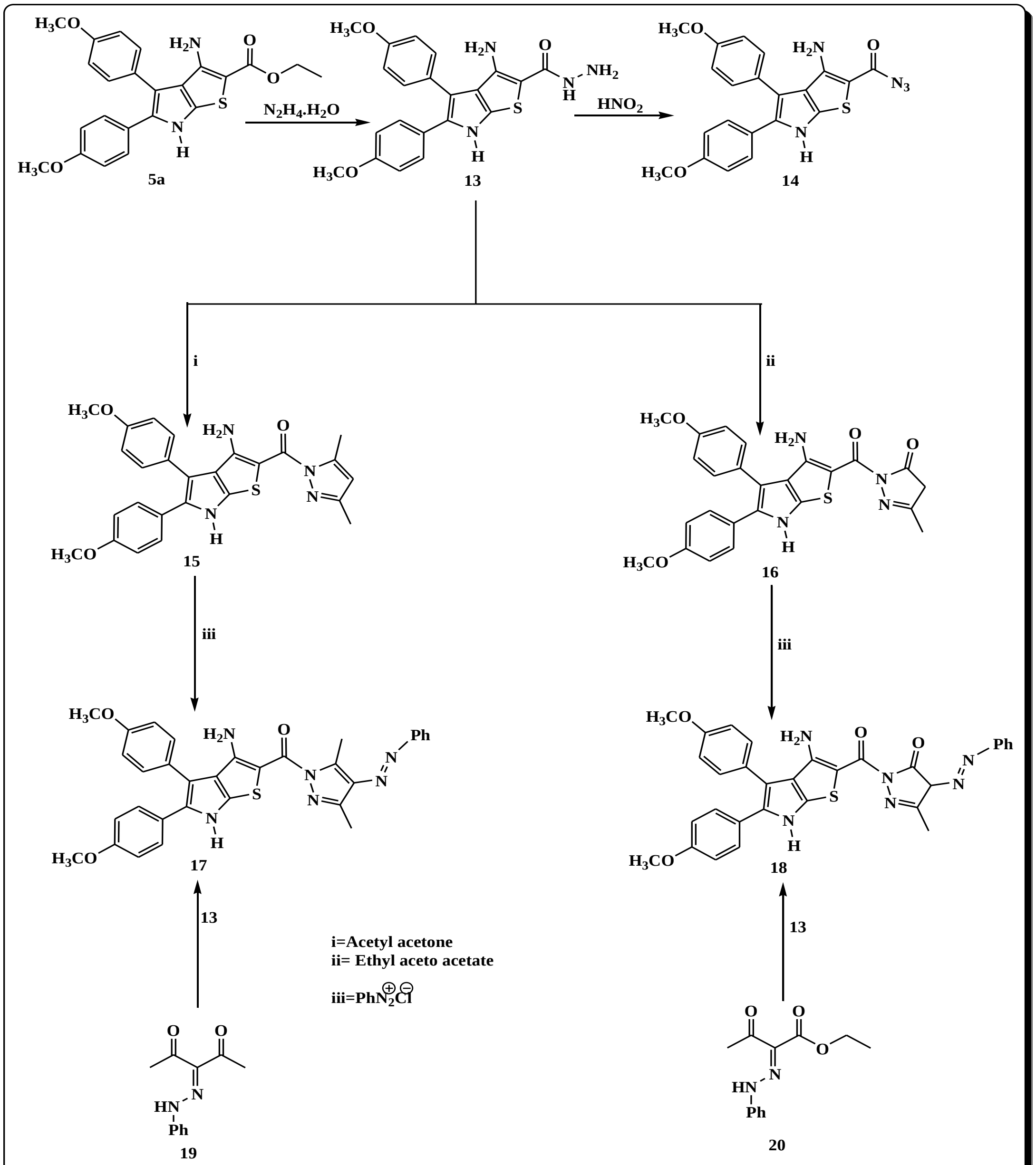
Scheme1.

Compound **5e** was boiled in formamide to afford **8**. On the other hand, it was converted to **6** *via* its reaction with triethyl orthoformate in acetic anhydride which was converted to **8** by its reaction with ammonia. Also, compound **6** reacted with hydrazine hydrate to afford **7** in a good yield. Boling of **5e** in formic acid afford the corresponding compound **9**, which was converted to the chloro derivative **10** by its reaction with phosphrous oxychloride. The chloro derivative converted to **11** *via* its reaction with hydrazine hydrate. The latter was converted to **12** by its reaction with nitrous acid at 0-5°C (Scheme2).



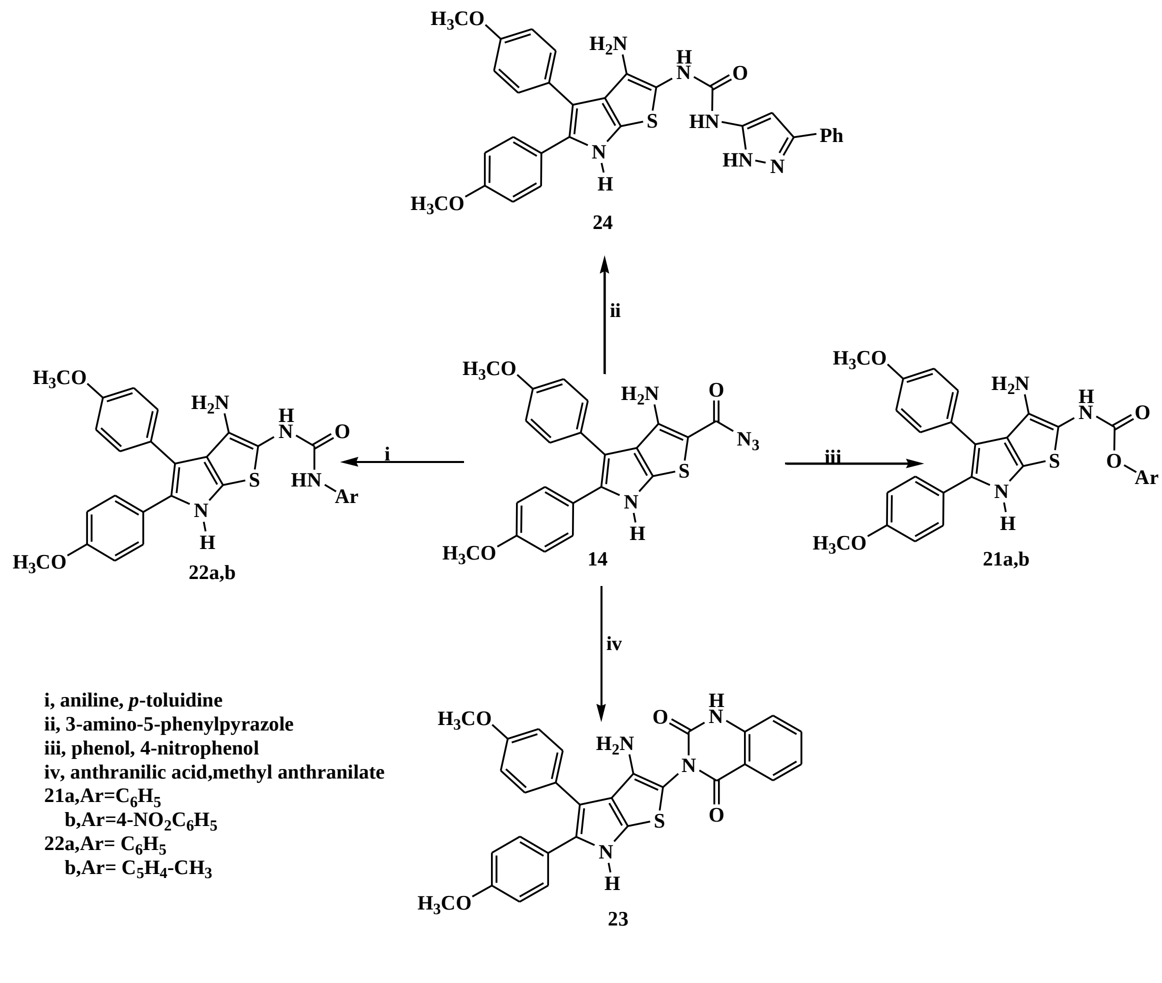
Scheme2.

Treatment of ethyl 3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrole-2-carboxylate (**5a**) with hydrazine hydrate gave 3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrole-2-carbohydrazide (**13**). Structure of **13** was confirmed by elemental analysis, spectral data and chemical transformation. Thus, **13** was reacted with nitrous acid, acetylacetone or ethyl acetoacetate to afford (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)azidomethanone (**14**), (3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrol-2-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (**15**) and 2-[3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrol-2-carbonyl]-5-methyl-2,4-dihydropyrazol-3-one (**16**), respectively. Structures **15** and **16** were elucidated on bases of elemental analysis, spectral data and chemical transformation. Thus, benzenediazonium chloride was reacted with **15** or **16** in ethanolic sodium acetate solution at 0-5°C to give **17**and **18**, respectively in good yields (Scheme 3).



Scheme3.

Finally, compound **14** reacted with each of aniline, *p*-toluidine, 3-amino-5-phenylpyrazole phenol, 4-nitrophenol, anthranilic acid and methyl anthranilate afforded urea derivatives **22** and **24**, aryl 3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrol-2-ylcarbamate(**21**) and 3-(3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrol-2-yl)quinazoline-2,4(1*H*,3*H*)-dione (**23**), respectively (Scheme 4).



Scheme4.

2. Biological Activity

Screening of antimicrobial activity was performed at a Microbiology Lab in Faculty of Agriculture, El-Azhar University, Cairo, Egypt. All the tested microorganisms were chosen on bases of their pathogenicity. Where, ***Aspergillus*** caused a broad spectrum of disease in the human host, ranging from hypersensitivity reactions to direct angioinvasion. ***Aspergillus*** primarily affects the lungs, causing 4 main syndromes, including allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing Aspergillus pneumonia (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. However, in patients who are severely immunocompromised, ***Aspergillus*** may hematogenously disseminate beyond the lung, potentially causing endophthalmitis, endocarditis, and abscesses in the myocardium, kidney, liver, spleen, soft tissue, and bone. On the other hand, ***Candida albicans*** is a diploid fungus that grows both as yeast and filamentous cells and a causal agent of opportunistic oral and genital infections in humans.[24][25]. ***C. albicans*** have emerged as important causes of morbidity and mortality in immunocompromised patients (e.g., AIDS, cancer chemotherapy, organ or bone marrow transplantation). Also, ***Staphlococcus aureus*** can cause a range of illnesses, from minor skin infections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), bacteremia, and sepsis. Its incidence ranges from skin, soft tissue, respiratory, bone, joint, endovascular to wound infections. It is still one of the five most common causes of nosocomial infections and is often the cause of postsurgical wound infections. Each year, some 500,000 patients in American hospitals contract a staphylococcal infection [26]. In addition, some ***Bacillus*** species can cause food poisoning; ***Bacillus*** can result in two different kinds of intoxications. It can either cause nausea, vomiting, and abdominal cramps for 1-6 hours, or diarrhea and

abdominal cramps for 8-16 hours. The food poisoning usually occurs from eating rice that is contaminated with ***Bacillus subtilis*** (EMBL EBI), Some ***Bacillus*** organisms can cause more severe illnesses, for example causes Anthrax. Also, ***Salmonella typhimurium*** is a pathogenic Gram-negative bacteria predominately found in the intestinal lumen. Its toxicity is due to an outer membrane consisting largely of lipopolysaccharides (LPS) which protect the bacteria from the environment. ***Salmonella typhimurium*** causes gastroenteritis in humans and other mammals. And finally, pathogenic strains of ***E. coli*** are responsible for three types of infections in humans: urinary tract infections (UTI), neonatal meningitis, and intestinal diseases (gastroenteritis). Representative derivatives **3**, **4a**, **4c**, **4f**, **5b**, **5d**, **5e**, **6**, **8**, **11**, **12**, **14**, **15**, **18**, **21a**, **22b, 23** and **24** were selected and tested for their antimicrobial activity against two gram(+) bacteria (*Staphlococcus aureus*, *Bacillus subtilis*), two gram(-) bacteria (*Escherichia coli*, *salmonella typhimurium*) and a filamentous fungus (*Asperigillus fumigatus*) and a diploid fungus (*Candida albicans*).using the modified Kirby-Bauer disc diffusion method [27][28][29]. For the disc diffusion, the zone diameters were measured with slipping calipers of the national committee for clinical laboratory standards [30].
The results are given in Table 1.

Table 1: Response of various microorganisms to some synthesized compounds in in vitro culture

Inhibition zone diameter (mm/mg sample) Antimicrobial activity%						
Sample	*A.fumigatus*	*C.albicans*	*S.aureus*	*B.subtilis*	*E.coli*	*S.typhimurium*
DMSO (positive control)	0.00	0.00	0.00	0.00	0.00	0.00
Tetracycline (Antibacterial agent)	--	--	30	29	31	30
Clotrimazole (Antifungal Agent)	24	22	--	--	--	--
3	10 42%	12 55%	11 37%	6 21%	0.00 0.00	0.00 0.00
4a	4 17%	10 45%	0.00 0.00	0.00 0.00	7 23%	5 17%
4c	0.00 0.00	0.00 0.00	12 40%	9 31%	0.00 0.00	0.00 0.00
4f	14 58%	19 41%	8 27%	4 14%	0.00 0.00	0.00 0.00
5b	6 25%	15 86%	0.00 0.00	0.00 0.00	9 29%	5 17%
5d	0.00 0.00	0.00 0.00	8 27%	3 10%	0.00 0.00	0.00 0.00
5e	8 33%	20 91%	21 70%	14 48%	15 48%	9 30%
6	15 63%	17 77%	15 50%	7 24%	0.00 0.00	8 27%
8	14 58%	17 77%	23 77%	16 55%	0.00 0.00	20 66%
11	19 79%	12 55%	5 17%	15 52%	4 13%	0.00 0.00
12	0.00 0.00	0.00 0.00	0.00 0.00	20 69%	9 29%	0.00 0.00
14	0.00 0.00	0.00 0.00	16 53%	12 41%	24 77%	12 40%
15	3 13%	8 36%	21 70%	0.00 0.00	0.00 0.00	7 23%
18	16 67%	5 23%	24 80%	10 34%	18 58%	16 53%

21a	12 50%	15 68%	16 53%	9 31%	14 45%	19 63%
22b	0.00 0.00	9 41%	0.00 0.00	12 41%	0.00 0.00	15 50%
23	0.00 0.00	0.00 0.00	17 57%	10 34%	12 39%	9 30%
24	4 17%	9 41%	21 70%	16 55%	5 16%	9 30%

Antimicrobial activity % = Inhibition zone diameter of the tested sample×100
Inhibition zone diameter of the standard

Strong effect means: antimicrobial activity% ≥ 60%
Moderate effect means: 60%>antimicrobial activity%≥40%
Weak effect means: 40%>antimicrobial activity%≥ 1%
No effect means: antimicrobial activity%=0.00%

3. Conclusion

The varied biological activities of the newly synthesized compounds promoted us to synthesize some new derivatives of these ring systems and study their antimicrobial activities. The antifungal activity studies revealed that compounds **6**, **11** and **18** show strong effects against Asperigillus fumigatusalso, also, compounds **5b, 5e, 6, 8** and **21a** show strong effects against Candida albicans. On the other hand compounds **5e, 8, 15, 18** and **24** display strong effects against Staphlococcus aureus. Compound **12** give strong effects against Bacillus subtilis. Compound **14** show strong effects against Escherichia coli. And finally compound **8** and **21a** afford strong effects against salmonella typhimurium. All the other compounds show effects against different types of tested microorganisms ranged from negative effects to moderate effects. So we can say that synthesis of new derivatives of these compounds is still an active area of research. Where, synthesis and study of the antimicrobial activities of new analogous of these compounds will be helpful for medicinal chemist to focus design of novel chemical entities containing pyrrole derivatives as a part of antimicrobial drugs.

4. Experimental

4.1. Experimental Instrumentation

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on shimadzu FT-IR 8201 PC spectrophotometer. H^1NMR was recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz FT-NMR system spectrometer and chemical shifts are expected in δ ppm units using TMS as an initial reference. Mass spectra were recorded on GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

4.2. Synthesis

4.2.1. 2,5-dihydro-4,5-bis(4-methoxyphenyl)-2-thioxo-1H-pyrrole-3-carbonitrile (3).

A mixture of 2-hydroxy-1,2-bis(4-methoxyphenyl) ethanone (**1**) (2.7 gm, 10 mmol) and cyanothioacetamide (1.0 gm, 10 mmol) was heated under reflux in ethanol (30 ml) containing catalytic amount of pipredine (10 drops) for 7 hrs. on cooling, the separated solid was filtered and recrystallized from benzene afforded **3** as orange crystals. **Yield:** 87%; **M.P.:** 220-222°C; **FT-IR (KBr, cm^{-1}):** 3429 (NH), 2206 (CN), 1631 (C=C), 1380 (C=S); **H^1NMR(300 MHz, DMSO-*d6*):** 3.31(s, 6H, $2CH_3$), 4.5(s, 1H, CH-pyrrole), 7.1-7.3 (m, 8H, Ar-H), 8.3 (s, 1H, NH, lost after D_2O exchange); **MS (El, m/z (%)):** 338(M+2, 4.7%), 337(M+1, 20.8%), 336(M^+, 79%) **Anal. Calcd. for$C_{19}H_{16}N_2O_2S$ (336):** C, 67.84; H, 4.79; N, 8.33 **Found:** C, 67.85; H, 4.79; N, 8.33.

4.2.2. 2-(Substituted thio)-4,5-bis(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile (4a-f).

A mixture of 2,5-dihydro-4,5-bis(4-methoxyphenyl)-2-thioxo-1*H*-pyrrole-3-carbonitrile (**3**) (1.85gm, 5 mmol), potassium hydroxide (0.28 gm, 5 mmol) in N,N-dimethylformamide (10 ml) was stirred for 2 hrs. the appropriate of ethyl chloroacetate, chloroacetone, ω-bromoacetophenone, ω-bromo-4-methylacetophenone, chloroacetonitrile or iodomethane (5 mmol) was added while stirring. Stirring was continued for 2 hrs. at room temperature the resulting solid was collected and recrystallized to afford the corresponding **4a-f**, respectively in good yields.

4.2.2.1. Ethyl 2-(3-cyano-4,5-bis(4-methoxyphenyl)-1H-pyrrol-2-ylthio)acetate(4a).

Pale yellow crystals from ethanol. **Yield:** 71%; **M.P.:** 156-158°C; **FT-IR (KBr, cm^{-1}):** 3421(NH), 2191(CN), 1731(C=O), 1589 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 1.28-1.33(t, 3H, CH_2**CH_3**), 3.28(s, 6H, $2CH_3$), 4.30-4.37(q, 2H, **CH_2**CH_3) 4.97(s, 2H,CH_2), 7.2-7.3(m, 8H, Ar-H), 8.39(s, 1H, NH, lost after D_2O exchange); **MS (El, m/z (%)):** 424 (M+2, 5.7%), 423 (M+1, 19%), 422 (M^+, 67%) **Anal. Calcd. for $C_{23}H_{22}N_2O_4S$ (422):** C, 65.38; H, 5.25; N, 6.63 **Found:** C, 65.37; H, 5.24; N, 6.63.

4.2.2.2. 2-(2-oxopropylthio)-4,5-bis(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile(4b).

Brown crystals from ethanol. **Yield:** 73%; **M.P.:** 132-134°C; **FT-IR (KBr, cm^{-1}):** 3398(NH), 2218(CN), 1697(C=O), 1593 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.8(s, 3H, CH_3), 3.28(s, 6H, $2CH_3$), 4.56(s, 2H,CH_2), 7.1-7.3(m, 8H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 394(M+2, 6%), 393(M+1, 25%), 392(M^+, 51%) **Anal. Calcd. for $C_{22}H_{20}N_2O_3S$ (392):** C, 67.33; H, 5.14; N, 7.14 **Found:** C, 67.33; H, 5.14; N, 7.14.

4.2.2.3. 4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-(2-oxo-2-phenylethylsulfanyl)-4-phenylnicotinonitrile (4c).

White crystals from ethanol. **Yield:** 72%; M.P.: 142-144°C; **FT-IR (KBr, cm^{-1}):** 3440(NH), 2191(CN), 1685(C=O), 1596 (C=C); **H^1NMR(300 MHz, DMSO-d6):** 3.33(s, 6H, $2CH_3$), 4.50(s, 2H,CH_2), 7.1-7.3(m, 13H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 456(M+2, 8%), 455(M+1, 29%), 454(M^+, 100%) **Anal. Calcd. for $C_{27}H_{22}N_2O_3S$ (454):** C, 71.34; H, 4.88; N, 6.16 **Found:** C, 71.34; H, 4.88; N, 6.17.

4.2.2.4. 4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-(2-oxo-2-p-tolylethylsulfanyl)-4-phenylnicotinonitrile (4d).

White crystals from ethanol. **Yield:** 78%; **M.P.:** 161-163°C; **FT-IR (KBr, cm^{-1}):** 3386(NH), 2210(CN), 1667(C=O), 1562 (C=C); **H^1NMR(300 MHz, DMSO-d6):** 2.56 (s, 3H, CH_3), 3.36 (s, 6H, $2CH_3$), 4.57(s, 2H,CH_2), 7.1-7.3(m, 12H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 470(M+2, 3%), 469(M+1, 36%), 468(M^+, 100%) **Anal. Calcd. for $C_{28}H_{24}N_2O_3S$ (468):** C, 71.77; H, 5.16; N, 5.98 **Found:** C, 71.77; H, 5.16; N, 5.98.

4.2.2.5. 2-(cyanomethylthio)-4,5-bis(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile (4e).

Off-white crystals from ethanol. **Yield:** 72%; **M.P.:** 151-153°C; **FT-IR (KBr, cm^{-1}):** 3398(NH), 2197(CN), 1600 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 4.50(s, 2H,CH_2), 7.1-7.3(m, 8H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 377 (M+2, 16%), 376 (M+1, 19%), 375(M^+, 70%) **Anal. Calcd. for $C_{21}H_{17}N_3O_2S$ (375):** C, 67.18; H, 4.56; N, 11.19 **Found:** C, 67.18; H, 4.56; N, 11.18.

4.2.2.6. 2-(ethylthio)-4,5-bis(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile (4f).

White crystals from ethanol. **Yield:** 92%; **M.P.:** 181-183°C; **FT-IR (KBr, cm^{-1}):** 3413(NH), 2187CN), 1627 (C=C); **H^1NMR(300 MHz, DMSO-d6):** 2.87(s,3H,CH_3), 3.33(s, 6H, $2CH_3$), 7.1-7.3(m, 8H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 352(M+2, 34%), 351(M+1, 56%), 350(M^+, 78%) **Anal. Calcd. for $C_{20}H_{18}N_2O_2S$ (350):** C, 68.55; H, 5.18; N, 7.99 **Found:** C, 68.54; H, 5.16; N, 7.99.

4.2.3. 4,5-bis(4-methoxyphenyl)-2-substituted-6H-thieno[2,3-b]pyrrol-3-amine (5a-e).

A mixture of the appropriate **4a-e** (5mmol) and catalytic amount of pipredine(5-7drops) in ethanol (20 ml) was boiled under reflux for 2hrs. the resulting solid was collected and recrystallized from acetic acid to give the corresponding thieno[2,3-*b*]pyrrole **5a-e**, respectively.

4.2.3.1. ethyl 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrole-2-carboxylate(5a).

Yellow crystals from acetic acid. **Yield:** 83%; **M.P.:** 241-243°C; **FT-IR (KBr, cm^{-1}):** 3421(NH), 3290,3170(NH_2), 1739(C=O), 1624 (C=N), 1512 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 1.28-1.33(t, 3H, CH_2**CH_3**), 3.5 (s, 6H, $2CH_3$), 4.30-4.37 (q, 2H, **CH_2**CH_3), 5.8 (s, 2H, NH_2, lost after D_2O exchange), 7.2-7.3(m, 8H, Ar-H), 8.63(s, 1H, NH, lost after D_2O exchange); **MS (El, m/z (%)):** 424(M+2, 5.7%), 423(M+1, 19%), 422(M^+, 67%) **Anal. Calcd. for $C_{23}H_{22}N_2O_4S$ (422):** C, 65.38; H, 5.25; N, 6.63 **Found:** C, 65.37; H, 5.24; N, 6.63.

4.2.3.2. 1-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)ethanone (5b).

Yellow crystals from acetic acid. **Yield:** 79%; **M.P.:** 230-232°C; **FT-IR (KBr, cm^{-1}):** 3390(NH), 3309,3200(NH_2), 1693(C=O), 1600 (C=C); **H^1NMR(300 MHz, DMSO-d6):** 2.7(s, 3H, CH_3), 3.31(s, 6H, 2CH_3), 5.35(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.9(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 394(M+2, 6%), 393(M+1, 25%), 392(M^+, 51%) **Anal. Calcd. for $C_{22}H_{20}N_2O_3S$ (392):** C, 67.33; H, 5.14; N, 7.14 **Found:** C, 67.33; H, 5.14; N, 7.14.

4.2.3.3. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(phenyl)methanone (5c).

Yellow crystals from acetic acid. **Yield:** 73%; M.P.: 260-262°C; **FT-IR (KBr, cm^{-1}):** 3406(NH), 3306,3286(NH_2), 1693(C=O), 1596 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, 2CH_3), 5.5(s, 2H,NH_2, lost after D_2O exchange), 7.1-7.3(m, 13H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 456(M+2, 8%), 455(M+1, 29%), 454(M^+, 100%) **Anal. Calcd. for $C_{27}H_{22}N_2O_3S$ (454):** C, 71.34; H, 4.88; N, 6.16 **Found:** C, 71.34; H, 4.88; N, 6.17.

4.2.3.4. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(p-tolyl)methanone(5d).

Yellow crystals from acetic acid. **Yield:** 91%; **M.P.:** 253-255°C; **FT-IR (KBr, cm^{-1}):** 3389(NH), 3217,3209(NH_2), 1662(C=O), 1589 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.56(s, 3H, CH_3), 3.36(s, 6H, 2CH_3), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 12H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 470(M+2, 3%), 469 (M+1, 36%), 468(M^+, 100%) **Anal. Calcd. for $C_{28}H_{24}N_2O_3S$ (468):** C, 71.77; H, 5.16; N, 5.98 **Found:** C, 71.77; H, 5.16; N, 5.98.

4.2.3.5. 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrole-2-carbonitrile(5e).

Yellow crystals from acetic acid. **Yield:** 89%; **M.P.:** 210-212°C; **FT-IR (KBr, cm^{-1}):** 3421(NH), 3128,3039(NH_2), 2214(CN), 1627 (C=C); **H^1NMR(300 MHz, DMSO-d6):** 3.33(s, 6H, 2CH_3), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 377(M+2, 16%), 376(M+1, 19%), 375(M^+, 70%) **Anal. Calcd. for $C_{21}H_{17}N_3O_2S$ (375):** C, 67.18; H, 4.56; N, 11.19 **Found:** C, 67.18; H, 4.56; N, 11.18.

4.2.4. N-[2-cyano-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrole-3-yl]formimidate(6).

A mixture of **5e** (3.75 gm, 10 mmol) and triethyl orthoformate(1.48 gm, 10 mmol) in acetic anhydride (20 ml) was heated under reflux for 10 hrs. the reaction mixture was poured onto ice (30 gm.). The resulting solid was collected and recrystallized from ethanol to give **6** as brown crystals. **Yield:** 67%; **M.P.:** 243-245°C; **FT-IR (KBr, cm^{-1}):** 3404(NH), 2978,2886(CH-aliphatics), 2208(CN), 1594 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 1.1-1.2(t, 3H, $CH_2\underline{\mathbf{CH_3}}$) 3.33(s, 6H, 2$CH_3$), 4.5(q, 2H, $\underline{\mathbf{CH_2}}CH_3$), 4,8(s, 1H, CH), 7.1-7.3(m, 8H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 433(M+2, 6%), 432(M+1, 8%), 431(M^+, 68%) **Anal. Calcd. for $C_{24}H_{21}N_3O_3S$ (431):** C, 66.80; H, 4.91; N, 9.74 **Found:** C, 66.80; H, 4.91; N, 9.73.

4.2.5. 5-Amino-4-imino-2,3-bis(4-methoxyphenyl)-8-thia-1,5,7-triazacyclopenta[a]indene (7).

A mixture of **6** (2.15 gm, 5 mmol) and hydrazine hydrate(1gm, 1ml, 20 mmol) was heated under reflux in ethanol (20 ml)for 3hrs. the resulting solid was collected and recrystallized from ethanol to afford **7** in a good yield. **Yield:** 89%; **M.P.:** 210-212°C; **FT-IR (KBr, cm^{-1}):** 3422,3370(NH), 3139,3072(NH_2), 1627 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, 2CH_3), 5.0 (s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.61(s, 1H, NH, lost after D_2O exchange), 9,5(s, 1H, CH-pyrimidine), 11.0(s, 1H, NH, lost after D_2O exchange); **MS (El, m/z (%)):** 419(M+2, 21%), 418(M+1, 53%), 417(M^+, 7%) **Anal. Calcd. for $C_{22}H_{19}N_5O_2S$ (417):** C, 63.29; H, 4.59; N, 16.78**Found:** C, 63.29; H, 4.59; N, 16.78.

4.2.6. 7-amino-2,3-bis(4-methoxyphenyl)-8-thia-1,4,6-triazacyclopenta[a]indene (8).

A mixture of **5e** (3.75gm, 10 mmol) and formamide (10 ml) was boiled under reflux for 10 hrs. the reaction mixture was poured onto ice (30 gm.). The resulting solid was collected and recrystallized from dioxane to give **8** as brown crystals. **Yield:** 67%; **M.P.:** >300°C; **FT-IR (KBr, cm^{-1}):** 3414(NH), 3209,3035(NH_2), 1627 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, 2CH_3), 5.5(s, 2H, NH_2), 7.1-7.3(m, 8H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange), 9.5(s, 1H, CH-pyrimidine); **MS(El, m/z (%)):** 404(M+2, 13%), 403(M+1, 79%), 402(M^+, 68%) **Anal. Calcd. for $C_{22}H_{18}N_4O_2S$ (402):** C, 65.65; H, 4.51; N, 13.92 **Found:** C, 65.65; H, 4.50; N, 13.92.

4.2.7. 2,3-bis(4-methoxyphenyl)-8-thia-1,4,6-triazacyclopenta[a]inden-7-one (9).

A mixture of **5e** (3.75 gm, 10 mmol) and formic acid (99%, 10 ml) was boiled under reflux for 10 hrs. the reaction mixture was poured onto ice (30gm.). The resulting solid was collected and recrystallized from DMF to give **9** as white crystals. **Yield:** 90%; **M.P.:** 270-272°C; **FT-IR (KBr, cm^{-1}):** 3448,3236 (NH),1697(C=O), 1566(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 7.1-7.3(m, 8H, Ar-H), 8.32(s, 1H, NH, lost after D_2O exchange), 10.05 (s, 1H, CH-pyrimidine), 12.0 (s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 405(M+2, 10%), 404(M+1, 0.76%), 403(M^+, 100%) **Anal. Calcd. for $C_{22}H_{17}N_3O_3S$ (403):** C, 65.49; H, 4.25; N, 10.42 **Found:** C, 65.49; H, 4.25; N, 10.42.

4.2.8. 7-Chloro-2,3-bis(4-methoxyphenyl)-8-thia-1,4,6-triazacyclopenta[a]indene (10).

A mixture of **9** (2 gm, 5 mmol) and phosphorus oxychloride (20 ml) was heated under reflux for 10 hrs. the reaction mixture was cooled and poured onto ice(50 gm.). the resulting solid was collected and recrystallized from acetic acid to afford **10** as grey crystals. **Yield:** 89%; **M.P.:** 240-242°C; **FT-IR (KBr, cm^{-1}):** 3428(NH),2930,2888 (CH-aliphatics), 1609(C=C), 1566(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.28(s, 6H, $2CH_3$), 7.1-7.3(m, 8H, Ar-H), 8.63(s, 1H, NH, lost after D_2O exchange), 10.02(s, 1H, CH-pyrimidine); **MS(El, m/z (%)):** 423(M+2, 19%), 421(M^+, 21%) **Anal. Calcd. for $C_{22}H_{16}ClN_3O_2S$ (403):** C, 62.63; H, 8.82; N, 9.96 **Found:** C, 62.63; H, 8.82; N, 9.96.

4.2.9. [2,3-bis(4-methoxyphenyl)-8-thia-1,4,6-triazacyclopenta[a]inden-7-yl]hydrazine (11).

A mixture of **10** (2 gm, 5 mmol) and hydrazine hydrate (1gm, 1ml, 20 mmol) was heated under reflux for 3 hrs. the resulting solid was collected and recrystallized from ethanol to give **11** as white crystals. **Yield:** 86%; **M.P.:** >300°C; **FT-IR (KBr, cm^{-1}):** 3439(NH), 3150,3107(NH_2), 3021(NH), 1697(C=O), 1596(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.32(s, 1H, NH, lost after D_2O exchange), 10.05 (s, 1H, CH-pyrimidine), 12.0 (s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 419(M+2, 10%), 418 (M+1,45%), 417(M^+, 7%) **Anal. Calcd. for $C_{22}H_{19}N_5O_2S$ (417):** C, 63.29; H, 4.59; N, 16.78 **Found:** C, 63.29; H, 4.59; N, 16.78.

4.2.10. 6,7-bis(4-methoxyphenyl)-9-thia-1,2,3,3a,5,8-hexaazacyclopenta[b]-as-indacene (12).

Saturated solution of sodium nitrite (10 ml) was added while stirring to a cold solution of **11** at 0-5°C in acetic acid (30 ml). the reaction was stirred for 1hr. the resulting solid was collected and recrystallized from acetic acid to give **12** as orange crystals. **Yield:** 82%; **M.P.:** 280-282°C; **FT-IR (KBr, cm^{-1}):** 3427(NH), 2935,2745(CH-aliphatics), 1596(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 7.1-7.3(m, 8H, Ar-H), 8.32(s, 1H, NH, lost after D_2O exchange), 10.05 (s, 1H, CH-pyrimidine); **MS(El, m/z (%)):** 430 (M+2, 5%), 429 (M+1,7%), 428 (M^+, 20%) **Anal. Calcd. for $C_{22}H_{16}N_6O_2S$ (428):** C, 61.67; H, 3.76; N, 19.61 **Found:** C, 61.67; H, 3.76; N, 19.61.

4.2.11. 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrole-2-carbohydrazide (13).

A mixture of ethyl 3-amino-4,5-bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrole-2- carboxylate (**5a**) (4.2 gm, 10 mmol) and hydrazine hydrate (1gm, 1 ml, 20 mmol) in ethanol (20 ml) was heated under reflux for 3hrs. the solid formed was collected and recrystallized from ethanol to give **13** as white crysals. **Yield:** 72%; **M.P.:** 260-262°C; **FT-IR (KBr, cm^{-1}):** 3371,3309 (NH_2), 3267,(NH), 3170,3024(NH_2), 2935,2856(CH-aliphatics), 1681(C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33 (s, 6H, $2CH_3$), 7.1-7.3 (m, 8H, Ar-H), 5.0(s, 2H, NH_2, lost after D_2O exchange), 6.4 (s, 2H, NH_2 lost after D_2O exchange), 8.32 (s, 1H, NH, lost after D_2O exchange), 11.08 (s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 410 (M+2, 5%), 409 (M+1,7%), 408 (M^+, 20%) **Anal. Calcd. for $C_{21}H_{20}N_4O_3S$ (408):** C, 61.75; H, 4.94; N, 13.72 **Found:** C, 61.74; H, 4.95; N, 13.73.

4.2.12. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)azidomethanone (14).

To a stirred solution of **13** (4gm, 10mmol) in hydrochloric acid (30 ml, 6M) at 0-5°C, sodium nitrite was added portion wise tell effervescence ended. The reaction mixture was stirred for 1hr. the resulting solid was collected, filtered, washed with water and recrystallized from acetic acid to give 14 as beige crystals. **Yield:** 88%; **M.P.:** 190-192°C; **FT-IR (KBr, cm^{-1}):** 3404 (NH), 3135,3021 (NH_2), 2935,2856(CH-aliphatics), 1689(C=O), 1612(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33 (s, 6H, $2CH_3$), 7.1-7.3 (m, 8H, Ar-H), 5.0 (s, 2H, NH_2, lost after D_2O exchange), 8.36(s, 1H, NH, lost after D_2O exchange),; **MS(El, m/z (%)):** 421(M+2, 15%), 420(M+1,1`2%), 419(M^+, 9%) **Anal. Calcd. for $C_{21}H_{17}N_5O_3S$ (419):** C, 60.13; H, 4.09; N, 16.70**Found:** C, 60.13; H, 4.09; N, 16.70.

4.2.13. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(5-substituted 3-methyl-1H-pyrazol-1-yl)methanone (15) and (16).

A mixture of **13** (2 gm, 5 mmol) and the appropriate of acetyl acetone or ethyl acetoacetate (5 mmol) in ethanol (20 ml) and acetic (5 drops) was heated under reflux for 3hrs. On cooling, the separated solid was collected and recrystallized from acetic acid to give **15,16**.

4.2.13.1. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone (15).

Color: White**; Yield:** 83%; **M.P.:** 218-220°C; **FT-IR (KBr, cm^{-1}):** 3460, 3359 (NH_2), 3062 (NH), 2974,2920(CH-aliphatics), 1686 (C=O), 1604 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.57(s, 3H, CH_3), 2.62(s, 3H, CH_3), 3.33(s, 6H, $2CH_3$), 5.52(s, 1H, CH-pyrazole, H-4), 6.05(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.36 (s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 474(M+2, 19%), 473(M+1,15%), 472(M^+, 9%) **Anal. Calcd. for $C_{26}H_{24}N_4O_3S$ (472):** C, 66.08; H, 5.12; N, 11.86 **Found:** C, 66.08; H, 5.12; N, 11.86.

4.2.13.2. 2-[3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-carbonyl]-5-methyl-2,4-dihydropyrazol-3-one (16).

Color: White**; Yield:** 89%; **M.P.:** 232-234°C; **FT-IR (KBr, cm^{-1}):** 3467, 3379 (NH_2), 3068 (NH), 2974,2920(CH-aliphatics), 1686, 1674(C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-d6):** 2.57(s, 3H, CH_3), 3.33(s, 6H, $2CH_3$), 4.0(dd, 1H, CH_2-pyrazole), 4.5(dd, 1H, CH_2), 6.05(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 8H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange),; **MS(El, m/z (%)):** 476(M+2, 32%), 475(M+1,14%), 474(M^+, 100%) **Anal. Calcd. for $C_{25}H_{22}N_4O_4S$ (474):** C, 63.28; H, 4.67; N, 11.81 **Found:** C, 63.28; H, 4.67; N, 11.81.

4.2.14. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(3,5-dimethyl-4-phenylazopyrazol-1-yl)methanone(17), 2-[3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-carbonyl]-5-methyl-4-phenylhydrazono-2,4-dihydropyrazol-3-one (18).

Method A: drop wise addition of benzenediazonium chloride (5 mmol), which was prepared via reaction of aniline (0.46 gm, 5mmol), hydrochloric acid (3ml, 6M) and sodium nitite (0.37 gm, 5 mmol) at 0-5°C to a mixture of the appropriate **15** or **16** and sodium acetate (0.41 gm, 5mmol) in ethanol (30 ml) while stirring. The reaction mixture was stirred for 3 hrs. the resulting solid was collected, washed with water and recrystallized from acetic acid to give **17** and **18**, respectively.

Method B: A mixture of **13** and the appropriate of 3-(2-phenylhydrazono)pentane- 2,4-dione (**19**) (5mmol) or ethyl 2-(2-phenylhydrazono)-3-oxobutanoate (**20**) (10 mmol) in ethanol (20 ml) and catalytic amount of acetic acid (2 drops) was refluxed for 2hrs.the resulting solid , so formed, was collected and recrystallized from acetic acid to give products identical in all aspects (M.P, IR, NMR, Mass and elemental analysis) with those obtained from method A.

4.2.14.1. (3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)(3,5-dimethyl-4-phenylazopyrazol-1-yl)methanone(17).

Color: White**; Yield:** 72%; **M.P.:** 260-262°C; **FT-IR (KBr, cm^{-1}):** 3460, 3372 (NH_2), 3069 (NH), 2974,2920(CH-aliphatics), 1689 (C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.57(s, 3H, CH_3), 2.63(s, 3H, CH_3), 3.33(s, 6H, $2CH_3$), 6.05(s, 2H, NH_2, lost after D_2O exchange), 7.12-7.3(m, 13H, Ar-H), 8.36(s, 1H, NH, lost after D_2O exchange),; **MS(El, m/z (%)):** 578(M+2, 18%), 577(M+1,9%), 576(M^+, 100%) **Anal. Calcd. for $C_{23}H_{28}N_6O_3S$ (576):** C, 66.65; H, 4.89; N, 14.57 **Found:** C, 66.65; H, 4.89; N, 14.57.

4.2.14.2. 2-[3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-carbonyl]-5-methyl-4-phenylhydrazono-2,4-dihydropyrazol-3-one (18).

Color: White**; Yield:** 81%; **M.P.:** 270-272°C; **FT-IR (KBr, cm^{-1}):** 3467, 3379 (NH_2), 3068 (NH), 2974,2920(CH-aliphatics), 1682, 1676(C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.57(s, 3H, CH_3), 3.33(s, 6H, $2CH_3$), 7.1-7.3(m, 14H, Ar-H), 6.05(s, 2H, NH_2, lost after D_2O exchange), 8.41(s, 1H, NH, lost after D_2O exchange),; **MS(El, m/z (%)):** 580(M+2, 32%), 579(M+1, 8%), 578(M^+, 100%) **Anal. Calcd. for $C_{31}H_{26}N_6O_4S$ (578):** C, 64.35; H, 4.53; N, 14.52 **Found:** C, 64.35; H, 4.53; N, 14.52.

4.2.15. Aryl 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-ylcarbamate (21a,b).

A mixture of the azido compound **14** (5 mmol) and the appropriate of phenol or p-nitrophenol (5 mmol) was heated under reflux for 5hrs. in dry benzene (20 ml). the resulting solid ,so formed, was collected and recrystallized from ethanol to give **21a** and **21b**, respectively.

4.2.15.1. phenyl 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-ylcarbamate (21a).

Color: brown**; Yield:** 81%; **M.P.:** 210-212°C; **FT-IR (KBr, cm^{-1}):** 3461, 3370 (NH_2), 3068 (NH), 2974,2920(CH-aliphatics), 1681(C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 7.1-7.3(m, 13H, Ar-H), 5.5(s, 2H, NH_2, lost after D_2O exchange), 8.41(s, 1H, NH, lost after D_2O exchange), 11.07(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 487(M+2, 32%), 486(M+1, 8%), 485(M^+, 100%) **Anal. Calcd. for $C_{27}H_{23}N_3O_4S$ (485):** C, 66.79; H, 4.77; N, 8.65 **Found:** C, 66.79; H, 4.77; N, 8.65.

4.2.15.2. 4-nitrophenyl 3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-ylcarbamate (21b).

Color: brown**; Yield:** 82%; **M.P.:** 230-232°C; **FT-IR (KBr, cm^{-1}):** 3443, 3370 (NH_2), 3060(NH), 2974, 2920(CH-aliphatics), 1682 (C=O), 1604(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 12H, Ar-H), 8.41(s, 1H, NH, lost after D_2O exchange), 11.09(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** **5**32(M+2, 32%), 531(M+1, 8%), **5**30(M^+, 100%) **Anal. Calcd. for $C_{27}H_{22}N_4O_6S$ (530):** C, 61.12; H, 4.18; N, 10.56 **Found:** C, 61.12; H, 4.18; N, 10.56.

4.2.16. 1-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)-3-arylurea (22a,b).

A mixture of the azido compound **14** (2 gm, 5 mmol) and the appropriate of aniline or *p*-toluidine (5 mmol) was heated under reflux for 5hrs. in dry dioxane (20 ml). the resulting solid ,so formed, was collected and recrystallized from ethanol to give **22a** and **22b**, respectively.

4.2.16.1. 1-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)-3-phenylurea(22a).

Color: beige**; Yield:** 78%; **M.P.:** 240-242°C; **FT-IR (KBr, cm^{-1}):** 3312, 3209 (NH_2), 3116,3109(NH), 1684 (C=O), 1609(C=C); **H^1NMR(300 MHz, DMSO-d6):** 3.33(s, 6H, $2CH_3$), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 13H, Ar-H), 8.43(s, 1H, NH, lost after D_2O exchange),11.09(s, 2H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 486 (M+2, 2%), 485 (M+1, 32%), 484 (M^+, 70%) **Anal. Calcd. for $C_{27}H_{24}N_4O_3S$ (484):** C, 66.92; H, 4.99; N, 11.56 **Found:** C, 66.92; H, 4.99; N, 11.56.

4.2.16.2. 1-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)-3-(4-nitrophenyl)urea(22b).

Color:beige**; Yield:** 72%; **M.P.:** 248-250°C; **FT-IR (KBr, cm^{-1}):** 3317, 3212 (NH_2), 3116, 3111(NH), 1682 (C=O), 1609(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.7(s,3H, CH_3), 3.33(s, 6H, $2CH_3$), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 12H, Ar-H), 8.43(s, 1H, NH, lost after D_2O exchange),11.09(s, 2H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 500 (M+2, 36%), 499(M+1, 33%), 498(M^+, 77%) **Anal. Calcd. for $C_{28}H_{26}N_4O_3S$ (498):** C, 67.45; H, 5.26; N, 11.24 **Found:** C, 67.45; H, 5.28; N, 11.25.

4.2.17. 3-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)quinazoline-2,4(1H,3H)-dione(23).

A mixture of the azido compound **14** (2 gm, 5 mmol) and the appropriate of anthranilic acid or methyl anthranilate (5 mmol) was heated under reflux for 5 hrs. in dry dioxane (20 ml). the resulting solid ,so formed, was collected and recrystallized from DMF to give **23** as white crystals. **Yield:** 92%; **M.P.:** >300°C; **FT-IR (KBr, cm^{-1}):** 3433(NH), 3317, 3212 (NH_2), 1681 (C=O), 1609(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 5.5(s, 2H, NH_2, lost after D_2O exchange), 7.1-7.3(m, 12H, Ar-H), 8.43(s, 1H, NH, lost after D_2O exchange),11.09(s, 1H, NH, lost after D_2O exchange); **MS(El, m/z (%)):** 512(M+2, 36%), 511(M+1, 33%), 510(M^+, 77%) **Anal. Calcd. for $C_{28}H_{22}N_4O_4S$ (510):** C, 65.87; H, 4.34; N, 10.97 **Found:** C, 65.87; H, 4.32; N, 10.97.

4.2.18. *1-(3-amino-4,5-bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrol-2-yl)-3-(3-phenyl-1H-pyrazol-5-yl)urea(24).*

A mixture of the azido compound **14** (2 gm, 5 mmol) and the 3-amino-5-phenylpyrazole (0.8 gm, 5 mmol) was heated under reflux for 5hrs. in dry dioxane (20 ml). the resulting solid ,so formed, was collected and recrystallized from ethanol to give **24** as white crystals. **Yield:** 71%; **M.P.:** 216-218°C; **FT-IR (KBr, cm^{-1}):** 3433, 3394(NH), 3319, 3221 (NH_2), 1681 (C=O), 1609(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 3.33(s, 6H, $2CH_3$), 5.49(s, 1H, pyrazole), 7.1-7.3(m, 13H, Ar-H), 6.5 (s, 2H, NH_2, lost after D_2O exchange), 8.43(s, 1H, NH, lost after D_2O exchange),11.32 (s, br, 3H, 3NH, lost after D_2O exchange); **MS(El, m/z (%)):** 552(M+2, 14%), 551(M+1, 45%), 550(M^+, 100%) **Anal. Calcd. for $C_{30}H_{26}N_6O_3S$ (550):** C, 65.44; H, 4.76; N, 15.26 **Found:** C, 65.46; H, 4.78; N, 15.28.

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