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Studies on synthesis and reactions of some new five and six-membered heterocycles bearing 5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-ones skeleton

Ahmed F. M. EL-Mahdy[a,b], Zeinab A. Hozien[a], Shimaa Abdelnaser[a], Ahmed A. K. Mohammed[a], Suliman M. El-Sawaisi[c], and Hassan A. H. El-Sherief[a]

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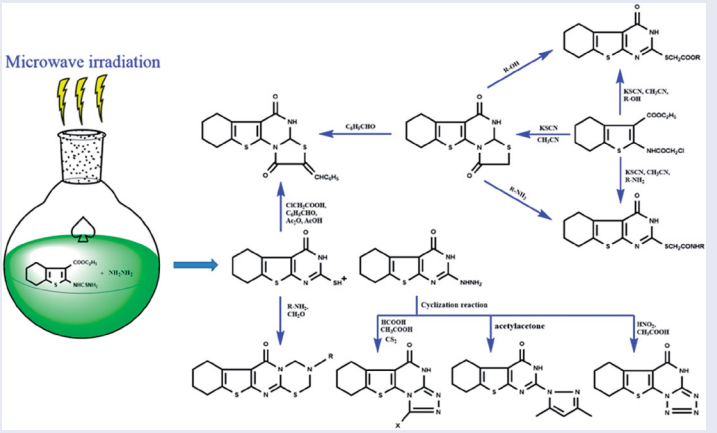
ABSTRACT

Thienopyrimidine derivatives are well-known in various pharmaceutical and biomedical domains. In this work, a series of efficacious and novel strategies for the synthesis of thienopyrimidines starting from 2-amino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene has been developed. The regioselectivity of these synthetic strategies was investigated using density functional theory computation and spectroscopic analysis. In addition, the chemical structures of the new thienopyrimidines and their reaction mechanisms, as well as the biological activity of selected compounds were studied.

GRAPHIC ABSTRACT



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KEYWORDS
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Introduction

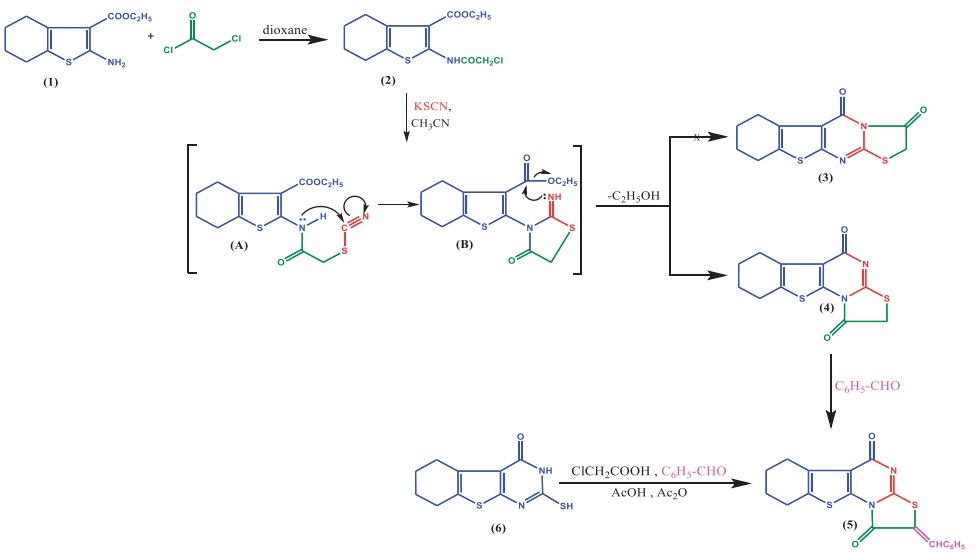
Pyrimidine and its derivatives have been received an attracting interest in medicinal research due to their biological processes and therapeutic uses.[1] Pyrimidine ring compounds showed numerous biological functions such as anti-inflammatory, antimicrobial, antibacterial, anti-inflammatory, anticancer, anticonvulsant, sedative, analgesic, antidepressant, and antipyretic agents.[1–7] Fused pyrimidines have also a wide range of pharmacological activity such as antitumor, anticancer, antihypertensive, antifolate and antioxidant.[7,8] In addition, antimalarial, antimicrobial, anti-inflammatory and analgesic activity in rats, antibiotic, antiviral influence, insecticide activity, and antimycotoxigenic activity are only a few of the pharmacological properties of thienopyrimidines.[9–13] Because of their important biological functions, the production of pyrimidine derivatives is an appealing scaffold in biomedical, pharmacology, and drug discovery sciences.

Mannich reaction is considered a very useful reaction because of its effectiveness in the generation of carbon-carbon and carbon-nitrogen covalent building linkers.[14] It is well documented that the Mannich reaction is usually used in the amino alkylation of various compounds with one or more active hydrogen atoms in the presence of primary amines and formaldehyde under mild conditions. Additionally, the double Mannich reaction has been reported as the reaction of compounds having two adjacent active hydrogens with primary amines and formaldehyde.[15–18] Recently, we have developed novel strategies for the synthesis of pyrimidothidiazine,[19] pyrazolopyrimidine,[20] triazolothidiazine,[21] thiadiazinobenzimidazoles,[22] pyrimidopyrimidinones[23] in high yields via double, triple and quadruple Mannich reactions.

As part of our continuing interest in the development of variously important compounds,[24–26] herein, we developed several approaches for the construction of thienopyrimidine derivatives starting from 2-amino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene. Fourier-transform infrared (FTIR), nuclear magnetic resonance (NMR), and elemental analyses were utilized to elucidate the chemical structures of the new compounds. The reaction regioselectivity and mechanism were also studied as well as the biological activity of such compounds.

Results and discussion

Reaction of 2-amino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene **(1)** with chloroacetyl chloride in dioxane produced 2-chloroacetylamino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene (**2**).[27] Herein we focused on the reaction of 2-chloroacetylamino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene (**2**) with potassium thiocyanate in acetonitrile, the reaction afforded a pure single product (TLC), which was identified as 1,2-dihydrothiazolo[3,2-a]-6,7,8,9-tetrahydrobenzo[b]thieno[3,2-e]pyrimidine-1,5-dione (**4**) rather than the other isomeric product 1,2-dihydrothiazolo[3,2-a]-6,7,8,9-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-3,5-dione (**3**). The formation of (**4**) could be explained via the formation of 2-thiocyanoacetyl-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene (**A**) which was transformed to 2-iminothiazolidine-4-one intermediate (**B**) followed by its cyclization to a tetracyclic compound (**4**) as shown in (Scheme 1). The intermediates (**A**) and (**B**) were separated in similar reactions,[28] however compound (**4**) was not separated previously. In addition, density

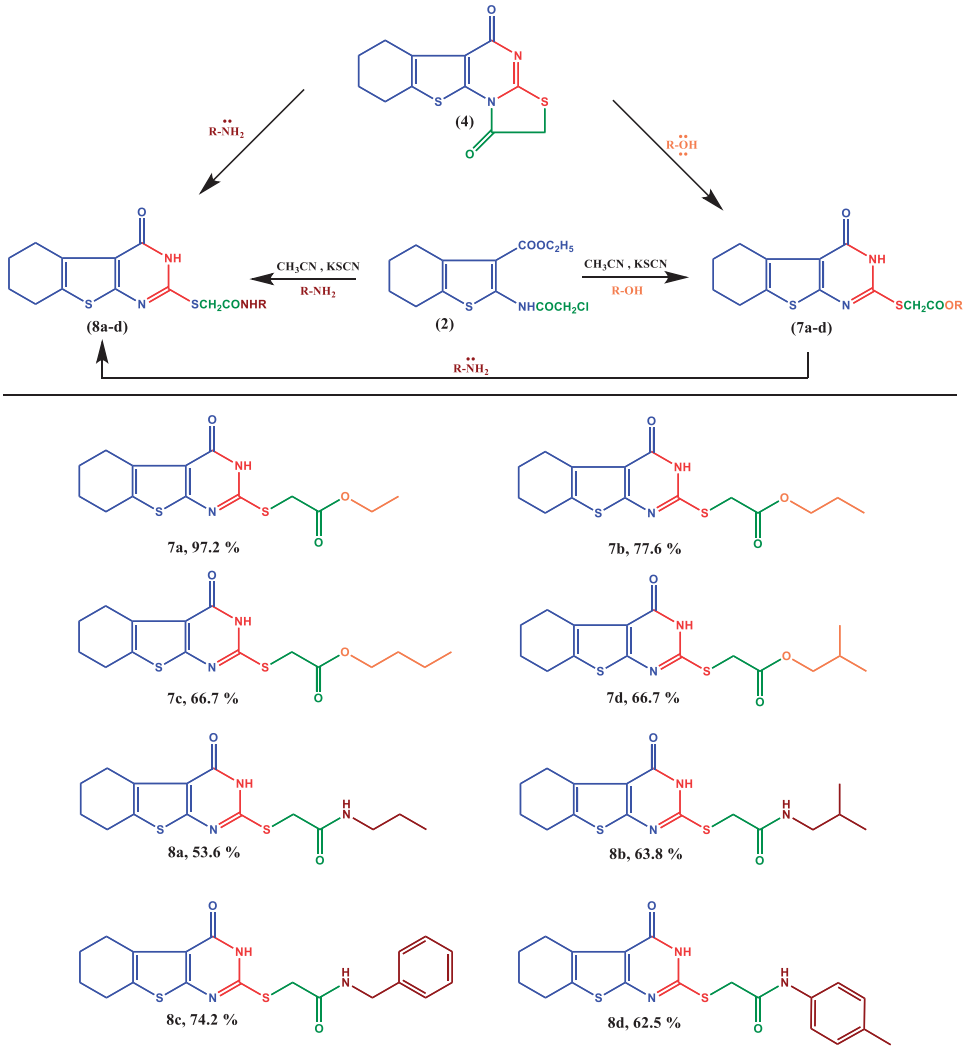


Scheme 1. Formation of 1,2-dihydrothiazolo[3,2-a]-6,7,8,9-tetrahydrobenzo[b]thieno[3,2-e]pyrimidine-1,5-dione (**4**) and 2-benzylidene-6,7,8,9-tetrahydrobenzo[b]thiazolo[3,2-a]thieno[3,2-e]pyrimidine-1,5-dione (**5**).

functional theory (DFT) calculations support the formation of isomer (**4**) rather than (**3**). As shown in Figure S21, the FTIR spectrum of **(4)** lacked the vibration bands over 3000 cm^{-1} and exhibited absorption bands at 2920–2840 cm^{-1} for the (C–H) aliphatic, at 1735 cm^{-1} for the (C = O) of thiazolidinone, and at 1650 cm^{-1} for the (C = O) of pyrimidinone ring. The ^{1}H-NMR spectrum of the reaction product (**4**) was characterized by the occurrence of a singlet signal at 3.84 ppm which attributed to the (CH_2) group of thiazolidinone moiety in addition to the other protons at the expected chemical shifts (Figure S22). Further, its mass spectrum and elementary analysis were found to be consistent with the proposed structure (Figure S23).

Scheme 1 also showed that 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (**6**) can be reacted with chloroacetic acid and benzaldehyde in a mixture of acetic acid/acetic anhydride to produce a single isolated product, which was identified as 2-benzylidene-6,7,8,9-tetrahydrobenzo[b]thiazolo[3,2-a]thieno[3,2-e]pyrimidine-1,5-dione (**5**). Due to the insolubility of product (**5**) in common NMR solvents, we confirmed its molecular structure chemically through the condensation of compound (**4**) with benzaldehyde under the same reaction condition. Both reactions gave similar products which having identical melting points, mixed melting point, and FTIR spectra (Figure S24). As shown in Figure S25, mass spectrum of the product (**5**) showed an expected molecular ion peak at (*m/z*) value of 366.65.

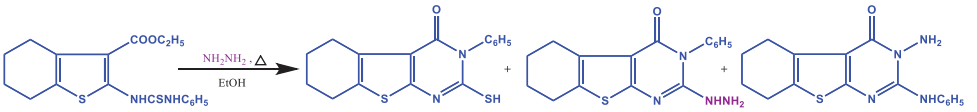
The reaction of (**2**) with KSCN in acetonitrile followed by the addition of suitable alcohols or primary amines afforded the corresponding esters (**7a–d**) and amides (**8a–d**), respectively. Further, refluxing of (**2**) with KSCN in boiling alcohols gave the corresponding esters (**7a–d**) directly, which can consider as a one-pot reaction for the synthesis of ester derivatives. The formation of these esters may be explained via the formation of (**4**) followed by nucleophilic attacking of alcohols. This assumption was confirmed by refluxing of (**4**) with the corresponding alcohols to give (**7a-d**). Further,



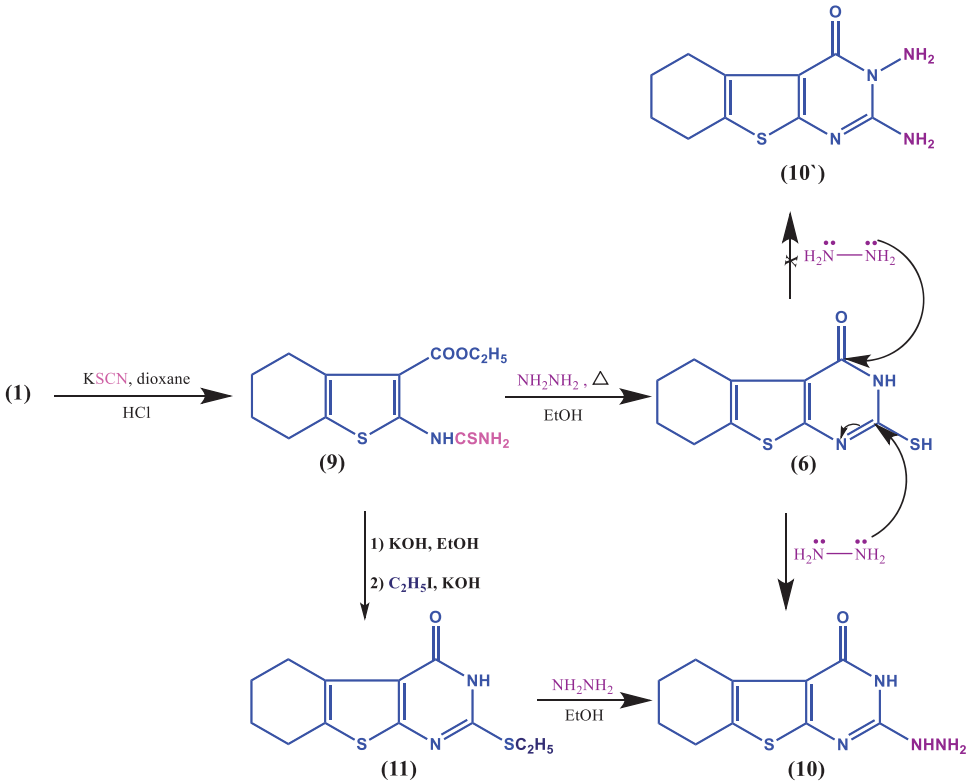
Scheme 2. One-pot reaction for synthesis of esters (**7a–d**) and amides (**8a–d**) derivatives.

refluxing of (**7a–d**) with suitable amines afforded the corresponding amides (8a-d) (Scheme 2).

Previously, Santagati et al. have been reported that the compound 3-amino-2-phenyl-amino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one was isolated as a single pure product by the refluxing of N-(3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]-thien-2-yl)-N-phenylthiourea with neat hydrazine hydrate (NH_2NH_2) or with NH_2NH_2 in ethanol.[29] Interestingly, El-Sherief et al. have reinvestigated this reaction and found that the refluxing of N-(3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-N-phenyl-thiourea with NH_2NH_2 yielded three products—2-hydrazino-3-phenyl-5,6,7,8-tetrahydrobenzo[b]thieno [2,3-d]pyrimidin-4(3H)-one, 3-amino-2-phenylamino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one and 2- mercapto-3-phenyl-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (Scheme 3).[30] To investigate a

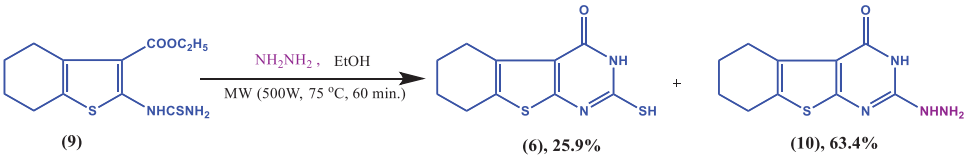


Scheme 3. Reactions of N-(3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-N-phenylthiourea with hydrazine hydrate.



Scheme 4. Mechanism of formation of 2-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (**10**).

similar reaction with N-(3-carboethoxy-4,5,6,7-tetrahydrobenzo[b] thien-2-yl)-N-thiourea (**9**), we firstly synthesized compound **9** through the treatment of **(1)** with KSCN in dioxane (Scheme 4). Treatment of (**9**) with NH_2NH_2 in ethanol produced 2-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (**10**) and 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one **(6)** as a mixed products (Scheme 4). Product **10** was isolated in 52.0% yield by cooling the reaction mixture followed by its isolation via a simple filtration, while compound **6** was isolated in 42.3% yield by the neutralization of the basic filtrate. The other isomeric product 2,3-diamino-5,6,7,8-tetrahydrobenzo [b]thieno[2,3-d]pyrimidin-4(3H)one **(10′)** not formed. The yield of the compound **6** was reduced either by utilization of the higher boiling solvent n-butanol instead of ethanol or by extending the reaction time. This action might be



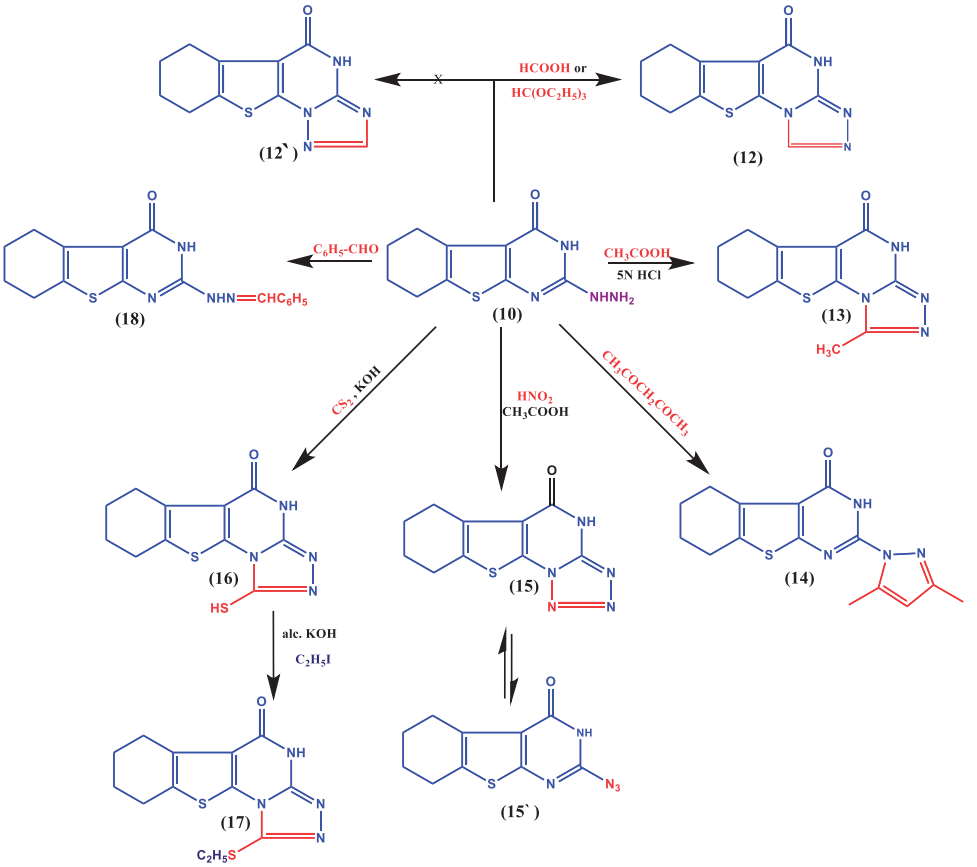
Scheme 5. Synthesis of 2-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (10).

attributed to the nucleophilic NH_2NH_2 attack on the electrophilic core C_2 that converted (**6**) to (**10**). This assumption was confirmed by treatment of S-alkylated compound **(11)** with NH_2NH_2 in a boiling ethanol to give **(10)** in 90.0% yield. Also, cyclization of N-(3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-N-thiourea **(9)** in a boiling alcoholic KOH yielded **(6)** in a high yield.

Over recent years, microwave irradiation had used as a powerful tool for the alternative heating sources due to certain advantages such as minimizing the energy consumption required for heating, reducing the reaction time, improving yield and purity of the products, operation simplicity, and avoiding a large quantity of solvents.[31,32] So, we repeated the reaction of (**9**) with hydrazine hydrate under microwave conditions of 500 W and 75 °C. The reaction was completed in few minutes (15 min) instead of a long time (10–50 hours) to give (**10**) and (**6**) in 52.8% and 35.0% yields, respectively (Scheme 5). However, the yield of (**10**) was increased to 63.4%, and (**6**) was decreased to 25.9% under microwave conditions of 500 W, 75 °C, and 60 minutes.

We then investigated the tolerance of compound (**10**) toward ring closure reactions with various reagents (Scheme 6). On the treatment of compound (**10**) with triethyl orthoformate or formic acid, the product 1,2,4-triazolo[4,3-a]-6,7,8,9-tetrahydrobenzo[b]thieno[3,2-e]pyrimidin-5-one (**12**) was formed rather than the other isomer (**12′**). In addition, the condensation of compound (**10**) with acetic acid and acetylacetone afforded 1-methyl-1,2,4-triazolo[4,3-a]-6,7,8,9-tetrahydrobenzo[b]thieno[3,2-e]pyrimidin-5-one (**13**) and 2-[3,5-dimethylpyrazol-1-yl]-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (**14**), respectively. Moreover, the reaction with HNO_2 gave the tetrazole derivative **(15)** which present in equilibrium with its azide form **(15′)**. Conversion of **(10)** to 1-mercaptotriazolo[4,3-a]thienopyrimidine **(16)** via its reaction with carbon disulfide in boiling alcoholic KOH, which was converted to **(17)** by refluxing with ethyl iodide in alcoholic KOH. Furthermore, the Shiff-base reaction of compound (**10**) with excessive benzaldehyde gave 2-benzylidenehydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one **(18)** (Scheme 6).

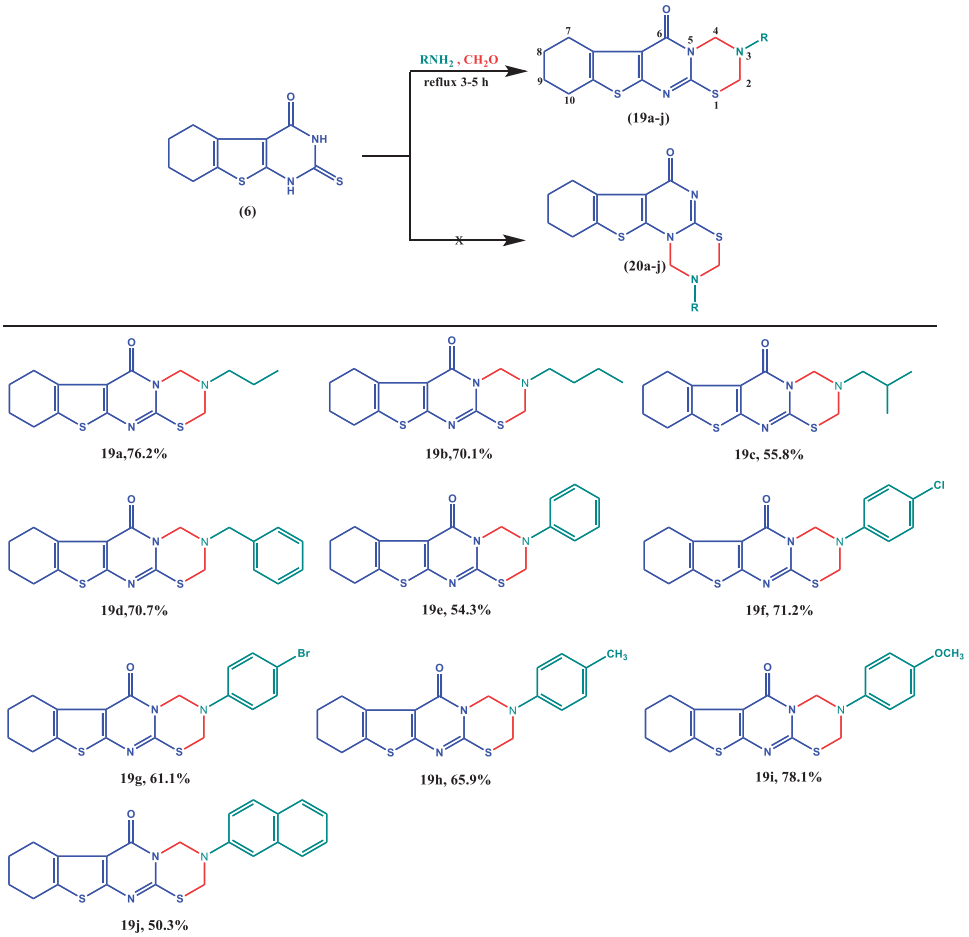
On the other hand, as a part of our ongoing interest in the synthesis of fused 1,3,5-thiadiazine heterocycles using Mannich type reaction.[19] We studied the susceptibility of 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one **(6)** as a polyfunctional nucleophile under Mannich reaction conditions. On Mannich condensation reaction of compound **(6)** with an equivalent of primary aliphatic, aromatic amine analogues and an aqueous formaldehyde (35%) in ethanol or dioxane for 3-5 h, the reaction may proceed to afford 3-N-substituted-7,8,9,10- tetrahydrobenzo[b]thieno [2,3-d]pyrimido[2,1-b]-1,3,5-thiadiazine-6-one **(19a–j)** or other possible isomeric products 3-N-substituted-7,8,9,10-tetrahydrobenzo[b]thieno[2,3-d]pyrimido[2,3-b]-1,3,5-



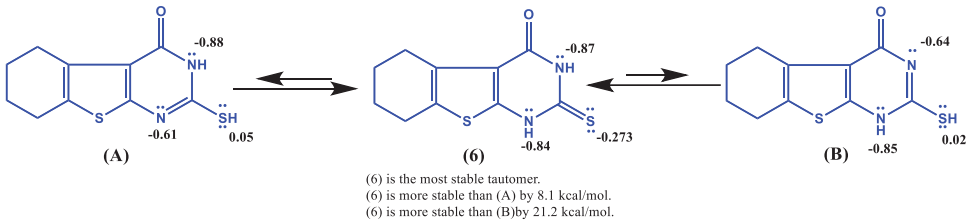
Scheme 6. Reactions of 2-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (10).

thiadiazine-11-one **(20a–j)** or a mixture of them. A simple TLC experiment indicated that such a reaction afforded only a single product (Scheme 7).

The FTIR spectra of the isolated products lacked the vibration band of the NH group and exhibited absorption bands at 2953–2832 cm^{-1} for the aliphatic (C–H), at 1671–1659 cm^{-1} for the (C = O), at 1558–1515 cm^{-1} for (C = N), and at 1498–1449 cm^{-1} for (C–S) of the thiadiazine ring. the ^{1}H-NMR spectra of the reaction products were characterized by the occurrence of two singlet signals at 5.5–4.6 and 5.8–5.1 ppm attributed to the aliphatic (CH_2) groups of thiadiazine moieties; SCH_2N and NCH_2N, respectively, in companied with the other protons at the expected chemical shifts. The mass spectra and elementary analyses of the double Mannich products were found to be consistent with the proposed structures. These findings cannot indicate which of these isomers **(19a–j)** or **(20a–j)** are the formed products, therefore, a solid argument is needed to confirm the formed isomeric products. This made us to think about the relative stability of tautomer A and B of compound **(6)** as well as the electronic charge density on N-1 and N-3. DFT calculations using Gaussian 09 program confirmed the higher stability of tautomer A as well as the highest electron density is located on N-3 than tautomer B (Scheme 8). Accordingly, tautomer A is more favorable

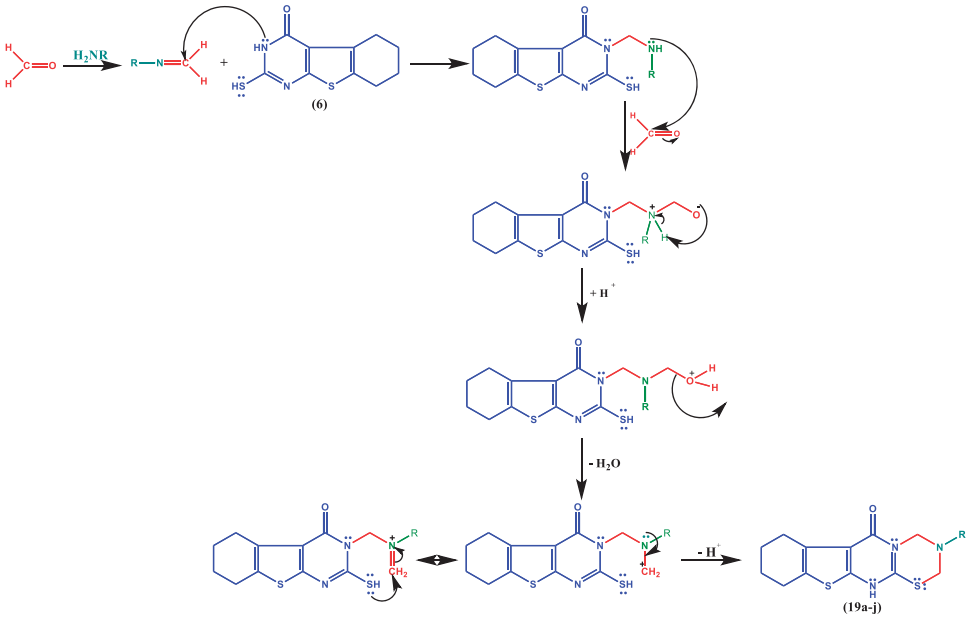


Scheme 7. Mannich reaction of 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (6).



Scheme 8. Tautomerism of 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one derivative (**6**).

to start Mannich reaction via N-3 to form (**19a–j**) rather than (**20a–j**) (Scheme 9). This assumption was supported by DFT calculations which confirmed the higher stability of isomer (**19a–j**) than (**20a–j**) (Figures S1–S20, Table 1). The energy difference between the derivatives of isomers (**19a–j**) and (**20a–j**) in kcal/mol were calculated using DFT at



Scheme 9. The suggested mechanism for formation of (**19a–j**).

Table 1 Energy difference between compounds (**19a–j**) and (**20a–j**).

Compound	R	(kcal mol^{-1})*
a	$CH_2CH_2CH_3$	15.58
b	$CH_2CH_2CH_2CH_3$	14.74
c	$CH_2CH(CH_3)_2$	17.67
d	$CH_2C_6H_5$	13.58
e	C_6H_5	14.18
f	C_6H_4Cl-*p*	14.41
g	C_6H_4Br-*p*	14.30
h	$C_6H_4CH_3$-*p*	14.04
i	$C_6H_4OCH_3$-*p*	13.55
j	2-naphthylamine	14.88

*$E_{20a-20j}$–$E_{19a-19j}$

the B3LYP-D3BJ/6-312G(d,p) level of theory. Isomer (**19a–j**) is more stable than all derivatives.

The generality of the Mannich reaction of compound (**6**) with primary aliphatic, aromatic amine analogues, was investigated. The primary aliphatic amines (propylamine, butylamine and isobutylamine) in addition to benzylamine produced the desired products (**19a–d**) in very good yields. Aliphatic amines are more active than aromatic amines. Therefore, aniline and 2-napthylamine gave the corresponding products (**19e** and **19j**) in good yields. Aromatic amines with electron-donating groups (*p*-methylaniline and *p*-methoxyaniline) gave the desired products (**19h** and **19i**) in very good yields, while aromatic amines with halides (*p*-chloroaniline and *p*-bromoaniline) produced the products (**19f** and **19 g**) in good yields. The fragmentation pattern of the compounds **(19a–j)** were found to be consistent with the proposed fragmentation pattern from A to E (Scheme 10) (Table S1).

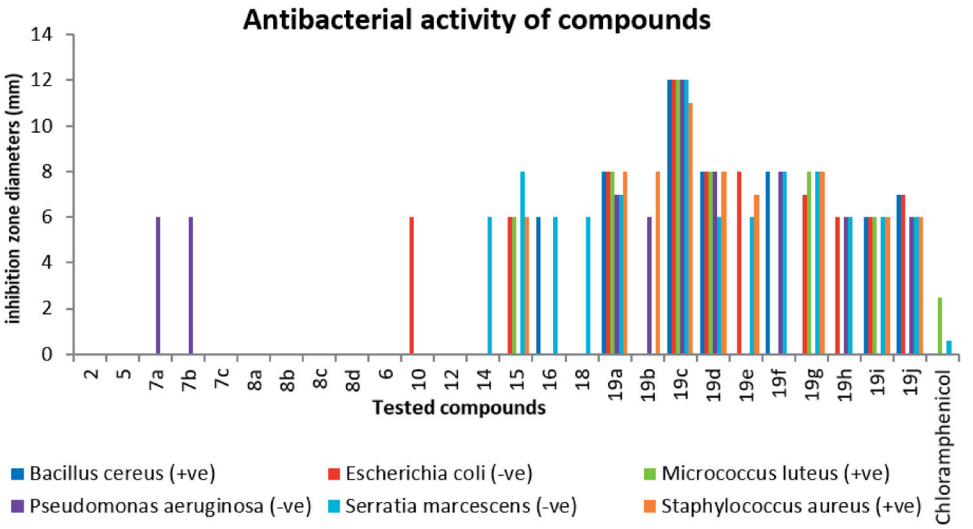
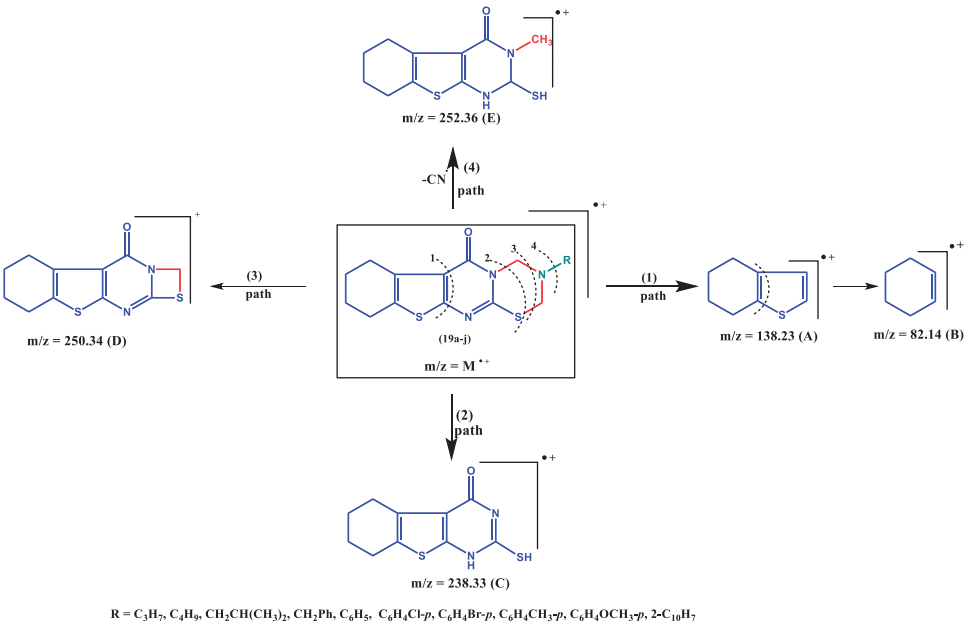


Figure 1. Comparison illustration of inhibition zone diameters for the antibacterial activity of our novel compounds at a concentration of 2.5 mg/0.1 mL.



Scheme 10. Fragmentation pattern of compounds (**19a–j**)

Antimicrobial activity

Pyrimidine derivatives have been shown to have a wide variety of antimicrobial properties.[33] Also, compounds containing a 1,3,5-thiadiazine moieties have been to possess antifungal properties.[34] The *in vitro* antimicrobial activity is divided into two categories; antibacterial and antifungal activities. The *in vitro* antimicrobial activities of our novel compounds were examined against six strains of bacteria, namely *Bacillus cereus*

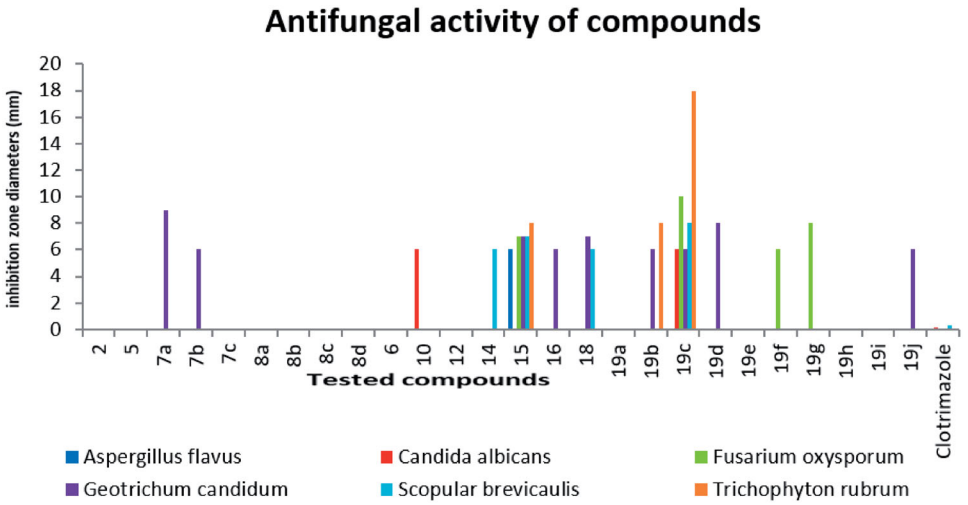


Figure 2. Comparison illustration of inhibition zone diameters for the antifungal activity of our novel compounds at a concentration of 2.5 mg/0.1 mL.

(+ve), *Escherichia coli* (−ve), Micrococcus luteus (+ve), *Pseudomonas aeruginosa* (−ve), *Serratia marcescens* (−ve) and *Staphylococcus aureus* (+ve) as well as six fungal species, namely *Aspergillus flavus, Candida albicans, Fusarium oxysporum, Geotrichum candidum, Scopular brevicaulis* and *Trichophyton rubrum* (Figures 1 and 2). New pyrimidine derivatives were synthesized and checked for antibacterial activities using the well diffusion method by measuring the zone of inhibition in millimeters. The inhibition zone diameters were clear agreement with good definition. The concentration of the tested compounds was 25 mg/ml and their inhibitions were measured at the end of 24 hours for bacteria by calculating the diameter of the inhibition region.[35] To measure the efficacy of the studied products under the same conditions, the references used Chloramphenicol as an antibacterial agent and Clotrimazole as an antifungal agent. Different compounds have varying antimicrobial action depending on the type of microorganism species and the compound itself.

Data from antibacterial and antifungal screening showed the following: the tested compound **(19c)** showed comparatively good activity against all the bacterial and fungal strains. Compounds **(2), (5), (7c), (8), (9)** and **(12)** showed no antibacterial activity, but compounds **(2), (5), (7c), (8), (9), (12), (19a), (19e), (19 h)** and **(19i)** exhibited no antifungal activity. The rest of compounds exhibited moderate antimicrobial activity. The finding results are depicted in (Table S2, S3).

Conclusions

In summary, we developed a series of efficacious and novel strategies for the synthesis of thienopyrimidines starting from 2-amino-3-carboethoxy-4,5,6,7-tetrahydrobenzo[b]-thiophene. Density functional theory computation and spectroscopic analyses were applied to investigate the regioselectivity of these synthetic strategies. The mechanisms and chemical structures of the final products were studied. Some of the synthesized compounds exhibited biological activities against different strains of bacterial and fungal

strains. The positive results obtained would allow for the fast synthesis of libraries of such derivatives for future modifications.

Experimental

Synthesis of 2-alkoxycarbonylmethylthio-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (7a-d) (general method)

Method A

A mixture of N-chloroacetyl derivative **(2)** (0.01 mol) and KSCN (0.03 mol) was refluxed in acetonitrile (50 ml) for 4 hours, followed by the addition of 10 ml suitable alcohol. The reaction mixture was cooled, poured into water, filtered to produce (**7a–d)** which washed with water several times, dried, and recrystallized from ethanol, to give **(7a–d)** in high yield.

Method B

Refluxing of a mixture of N-chloroacetyl derivative **(2)** (0.01 mol) and KSCN (0.03 mol) in a suitable alcohol (20 ml) for 4 hours, gave the same products of method A. Compound **(7a)** was also obtained by refluxing **(6)** (0.01 mol) with ethyl chloroacetate (0.012 mol) in ethanol (50 ml) for 3 hours in high yield and the product was identical with those obtained by method A and B, in terms of melting point (296 °C), mixed melting point, TLC and spectral analysis.

Synthesis of 2-carboxamidomethylthio-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one (8a–d) (general method)

Method A

A mixture of N-chloroacetyl derivative **(2)** (0.01 mol) and KSCN (0.03 mol) was refluxed in CH_3CN (50 ml) for 4 hours, followed by the addition of appropriate amine (0.012 mol). After cooling, the solid was collected, rinsed with water, dried, and crystallized from ethanol to produce **(8a–d)** in high yields.

Method B

A mixture of ester derivative **(7a–d)** (0.01 mol) and appropriate amine (0.012 mol) was heated in ethanol (50 ml) until boiling for 3 hours. After cooling, the solid was collected, rinsed with water, dried, and crystallized from ethanol to produce **(8a–d)** in high yields.

Synthesis of 3-N-substituted-7,8,9,10-tetrahydrobenzo[b]thieno[2,3-d]pyrimido[2,1-b]-1,3,5-thiadiazine-6-one (19a–j) (general method)

General procedure. 2-mercapto-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one **(6)** (0.001 mol), appropriate aliphatic or aromatic primary amines (0.0011 mol) and formaldehyde (2 ml) was refluxed in ethanol or ethanol/dioxane mixture (20 ml) for 3–5 hours. The resultant precipitate was obtained by filtration, treated several times with water, and thoroughly dried. To obtain the final product **(19a–j)** as colorless or yellow

needles in 50–78% yield, the crude product was crystallized from the appropriate solvent.

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