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TO STUDY THE SYNTHESIS OF SOME NEW HETEROCYCLES BASED ON PHENOTHIAZINE MOIETY AND THEIR BIOLOGICAL APPLICATIONS

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ABSTRACT

Heterocycles containing nitrogen have a wide range of uses in various branches of chemistry. A wide range of biological functions are provided by nitrogen-based heterocycles; the lone pair in nitrogen atoms serves as a donor, making it easier to create different supramolecular blocks. Functionalized nitrogen heterocycles are essential to medical and pharmaceutical chemistry. Drug design and development has made extensive use of them. A significant family of organic reactions known as multi-component reactions (MCRs) uses three or more numbered starting components to create various target molecules in a single pot reaction. Because MCR-based reactions eliminate multistep reactions for combinatorial and parallel synthesis and have the advantages of single flask reaction conditions, efficiency, and lower cost, both academic and industrial researchers have been working on their development for the past ten years. The synthesis of dihydropyrimidines via a straightforward one-pot cyclocondensation process of ethyl acetoacetate, benzaldehyde, and urea was reported by Italian scientist Pietro Biginelli in 1893. By isolating intermediates and eliminating multistep, multi-component reactions have the benefit of having shorter reaction times and higher product yields.

KEYWORD: Heterocycles, Multi-Component, Nitrogen, Academic

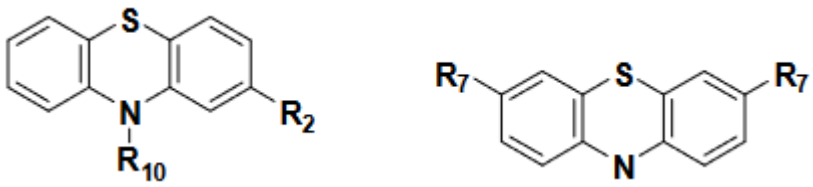
1. INTRODUCTION

Due to possible uses, the chemistry of aromatic molecules with nitrogen-sulfur heteroatoms is being investigated as a primary field of study. One of the main methods for creating new chemically active

chemicals, such as natural alkaloids, is to combine two or more pharmacophores in a single molecule. Of all the medications, compounds having heterocyclic structural components are the most common. Among the various heterocyclic derivatives, molecules with a broad range of biological activity that contain sulfur and nitrogen hold a distinct place.

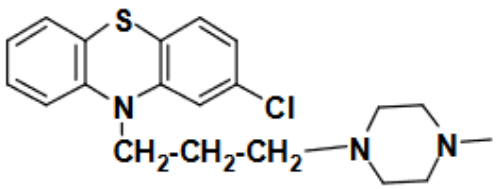
As an insecticide and antihelmintic medication, for instance, phenothiazine with a condensed tricyclic system is highly beneficial (Elderfield et al., 1957). Bernthsen obtained the parent chemical, 10H-dibenzo-1,4-thiazine, for the first time in 1883 (Bernthsen, 1883). Phenothiazine derivatives are a class of chemicals that have a distinctive tricyclic aromatic ring with nitrogen and sulfur atoms and substituents in the 2 and 10 or 3 and 7 positions: Commonly used as antipsychotropic and antihistaminic medications, phenothiazine positions are anticholinergic derivatives that have been substituted in positions 2 and 10 (Gupta et al., 1988).

Because of their pharmacological activity, these substances have been the subject of extensive research in a variety of disciplines, including chemical, biological, and medical. Numerous phenothiazine derivatives are also utilized in analytical chemistry, particularly those that are substituted at positions 3 and 7 (dyes of the Methylene Blue group). Additionally, compounds that are substituted at positions 10 and 2 and 10 are used as a redox indicator, a peroxide generator, in sulfide analysis, and in water testing. Due to the current global interest in this family of chemicals, a large body of research has been produced about the stability and analysis of phenothiazines (Tiago et al., 2006).

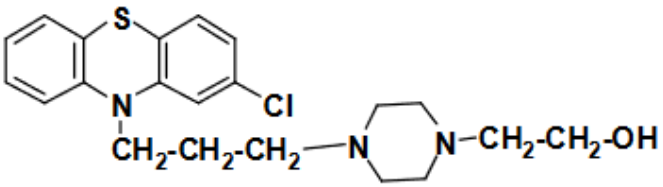


In addition to being salts such as hydrochlorides, maleates, tartrates, and dimethylsulfonates, phenothiazine derivatives can also exist as free bases. Yellow, greasy liquids that are insoluble in water are the free bases. The white, crystalline salts of the phenothiazine derivatives dissolve readily in water, diluted aqueous hydrochloric acid, and other organic solvents. According to differences in their chemical structure, pharmacological actions, and potency, phenothiazines—which are commonly used as neuroleptics in the treatment of schizophrenia, organic psychoses, the manic phase of manic-depressive illness, and other acute or chronic idiopathic psychotic illnesses—are classified into three subclasses: aliphatic, piperazine, and

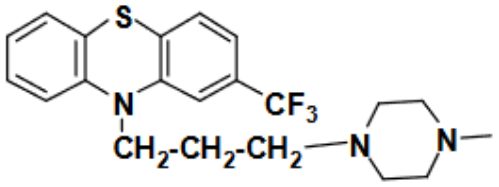
piperidine (Foye et al., 1995). Compared to other groups like chlorine and trifluoromethyl, the piperazine subclass has strong antipsychotic action with more noticeable extrapyramidal effects but less anticholinergic and sedative effects (Conradie et al., 1988). This study focuses on four structurally related piperazine-substituted phenothiazine derivatives: prochlorperazine, perphenazine, trifluoperazine, and fluphenazine.



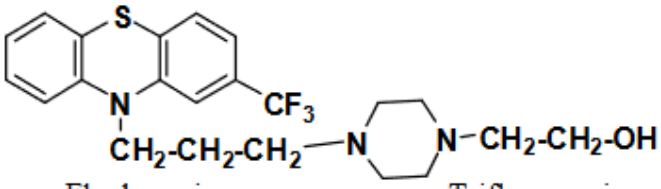
Perphenazine



Prochlorperazine



Fluphenazine



Trifluoperazine

As a marker for proteins and DNA, phenothiazine has recently gained a lot of popularity in material science and biology (Nakadan et al., 2004). According to reports, the phenothiazine drugs' therapeutic action entails blocking dopamine receptors in the brain (Richard et al., 1974; Hom et al., 1975). The side chain and substituent interact to increase the phenothiazines' capacity to mimic dopamine's preferred trans alpha conformation.

1.1 OBJECTIVES OF THE STUDY

1. Synthesis of Some New Heterocycles Based on Phenothiazine Moiety and their Biological Applications.
2. Ultrasound Assisted Synthesis of Pyrimidine Carboxamides Catalyzed by UO2(NO3)2.6H2O and their Biological Studies.

2. REVIEW OF LITERATURE

Aydogan, N., Z. Ocal, Turgut and C. Yolacan (2020) observed that the Metal complexes are important in nature and have been widely employed in therapeutic applications as enzyme inhibitors, antibacterial, antiviral, and anticancer [62-64]. Adenine (A) metal complexes have been found to exhibit anticancer action. With nitrogen and sulphur as donor atoms, N-substituted phenothiazines are good electron donors and have been reported to exhibit antiserotonin, antihistaminic, and anticonvulsant properties. We intend to synthesise N-substituted phenothiazines and metal phenothiazines, as well as their transition metal complexes, due to the multifarious properties of N-substituted phenothiazines and metal phenothiazines as fungicides and bactericides. Psychotherapeutic, antituberculosis, antiemetic, and antihistamine medicines are all made from N-alkyl phenothiazine. The pharmacological actions of N-alkyl phenothiazine are due to the N-alkyl amine side chains. Drugs of the phenothiazine class have a wide range of biological effects.

Phenothiazine is widely used in industry as an antioxidant to avoid oxidative changes in polyethylene oils. Phenothiazines are utilised as stabilisers in the treatment of polyester fibres, lubricating greases, polycarbamates, and polyether-based urethane rubbers. Bis (amides) produced by reacting phenothiazine with one equivalent of a dicarboxilic acid reduce corrosion of metals in contact with petroleum fractions other than gasoline. Photo ionisation research for solar energy conversion processes have recently sparked a lot of interest in phenthiazine.

Bata, A.B., J.H. Kalin, E.M. Fooksman, E.L. Amorose, C.M. Price, H.M. William, M.J. Rodig, M.O. Mitchell, S.H. Cho, Y. Wang and S.G. Franzblau (2017) observed that the Phenothiazines have been utilised as gravimetric and spectrophotometric reagents, as well as redox and metal ion indicators, in the field of chemical analysis. In several fungicides, the role of toxicity in compounds containing nitrogen and sulphur atoms has been well demonstrated. In psychiatry and chemotherapy, N-alkyl phenothiazines with both sulphur and nitrogen as coordinating atoms are commonly utilised as tranquillizers. They have low ionisation potentials and have been discovered to be good electron donors. In terms of synthesis of new metal complexes, related derivatives, investigating their characteristics, and uses, N-substituted phenothiazines have a wide range of applications.

3. RESEARCH METHODOLOGY

In a 50 mL two-necked round bottom flask, phenothiazine (1.0 mmol), iodoethane or iodomethane (3.0 mmol), and DMF (30 mL) were added. The solution was heated to 75°C, then treated with potassium tert-

butoxide (1.5 mmol) in portions and agitated for 24 hours at 80°C. The reaction mixture was cooled to room temperature and put into ice water when the reaction had completed (as monitored by TLC), and then extracted with chloroform (75 mL) and dried over Na2SO4. The crude gelly-like material obtained by removing the solvent was refined using hexane/ethyl acetate (4:1) column chromatography to yield 2 (a-b) as a white solid (yield: approx. 80 percent).

3.2 PROCEDURE FOR THE PREPARATION OF 10-ALKYL-3-FORMYL PHENOTHIAZINE 3(a-b):

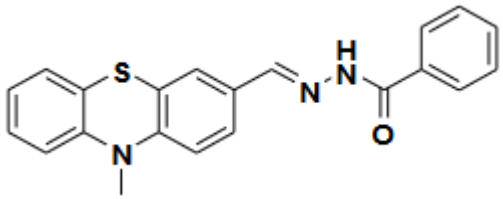
Phosphorus oxychloride (POCl3) (4.1 mmol) was added dropwise at 0°C under nitrogen atmosphere to 4.7 mmol of newly distilled N,N-dimethylformamide in a two neck round bottom flask. At 30oC, a dropwise addition of (1.0 mmol) N-alkyl-phenothiazine 2(a-b) dissolved in dichloroethane 30 mL was made to the POCl3/DMF complex. At 80°C, the reaction mixture was stirred for 16 hours. The reaction mixture was cooled to room temperature and dumped into ice water once the reaction was completed (as determined by TLC). After neutralising the mixture with NaHCO3, it was extracted with chloroform (75 mL) and dried over Na2SO4. Vacuum distillation was used to evaporate the solvent. The crude product was refined using hexane/ethyl acetate (3.5:1.5) column chromatography, yielding a product with a purity of 78-81 percent.

4. DATA ANALYSIS AND RESULTS

In a 50 mL beaker, 10 mL of methanol and 0.5 (mL) of glacial acetic acid were combined with an equimolar quantity of 10-alkyl-10H-phenothiazine-3-carbaldehyde 3(a-b) (1 mmol) and heterocyclic acetohydrazide 4(a-f) (1 mmol). A 3 mm wide by 140 mm long probe, which was submerged directly into the reaction mixture for varying periods of time as indicated in Table 1, was used to subject the mixture to ultrasound irradiation using an ultrasonic processor (to avoid increase vapor pressure of ethanol and to achieve effective cavitations in this solvent). With manual adjustment, the output power was 104 watts, and the working frequency was 16 kHz. Thin layer chromatography was used to track the reaction's development. The appropriate Schiff base 5(a-k) derivatives were obtained by cooling the combination to room temperature, filtering out the separated solid, washing it with 40 mL of excess methanol, and then letting it dry at room temperature.

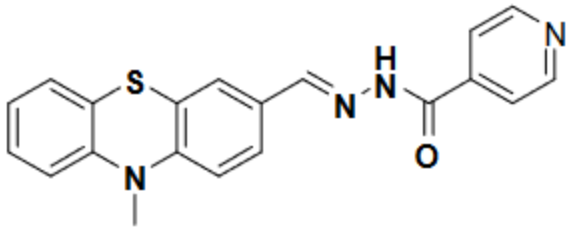
N'-((10-methyl-10H-phenothiazin-3-yl)methylene)benzohydrazide **(5a):**

The reaction was conducted using the general protocol described in 1.4.4 after an equimolar amount of compound 3a (1 mmol) and benzohydrazide (1 mmol) were introduced to 10 mL of methanol and 0.5 mL of glacial acetic acid. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 212-215ºC; IR (KBr) vmax: 3446, 3188, 3026, 2960, 2924, 2850, 1903, 1645, 1602, 1570, 1460, 1400, 1288, 1220, 1138, 1076 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH = 11.77 (s, 1H, NH), 8.35 (s, 1H, N=CH), 7.91 (d, 2H, J = 7.5Hz, o & o'- Ar-H of phenyl ring), 6.99- 7.59 (m, 10H, Ar-H of phenyl and phenothiazine ring), 3.36 (s, 3H, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC = 163.4, 147.2, 147.2, 145.0, 134.0, 132.1, 129.2, 128.9, 128.4, 128.0, 127.6, 127.3, 125.2, 123.0, 121.9, 115.4, 115.1, 35.8; HRMS (EI): m/z [M+] calcd. for C21H17N3OS: 359.1092; found: 359.1061.



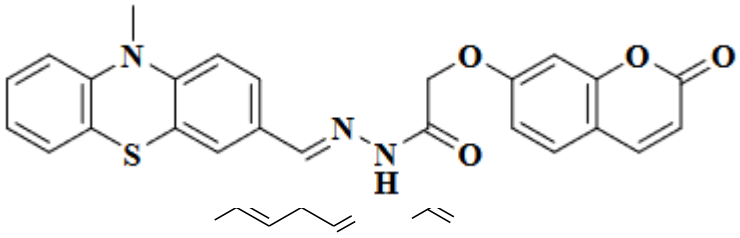
N'-((10-methyl-10H-phenothiazin-3-yl)methylene)isonicotinohydrazide (5b):

Compound 3a (1 mmol) and isonicotinohydrazide (1 mmol) were introduced in an equimolar amount to 10 mL of methanol and 0.5 mL of glacial acetic acid. The reaction was then conducted in accordance with the general protocol provided in 1.4.4. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 218-220ºC; IR (KBr) vmax: 3423, 3250, 3070, 3032, 2872, 2816, 1654, 1595, 1546, 1465, 1406, 1334, 1292, 1255, 1222, 1143, 1064 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH = 11.99 (s, 1H, NH), 8.79 (dd, 2H, J = 1.75 & 4.25 Hz, C2 & C6- Ar-H of nicotine ring), 8.36 (s, 1H, N=CH), 7.82 (dd, 2H, J = 2.0 & 4.5Hz, C3 & C5 - Ar-H of nicotine ring), 7.58 (dd, 1H, J = 1.75 & 8.25 Hz, C2 - Ar-H of phenothiazine ring), 7.52 (d, 1H, J = 2.0 Hz, C4 - Ar-H of phenothiazine ring), 6.98-7.24 (m, 5H, Ar-H of phenothiazine ring), 3.36 (s, 3H, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC = 161.9, 150.7, 149.9, 148.4, 147.4, 144.9, 141.3, 128.8, 128.4, 127.8, 127.3, 125.4, 123.4, 123.0, 121.9, 121.9, 115.4, 115.1, 35.8; HRMS (EI): m/z [M+] calcd. for C20H16N4OS: 360.1045; found: 360.1044.



N'-((10-methyl-10H-phenothiazin-3-yl)methylene)-2-(2-oxo-2H-chromen-7- yloxy)acetohydrazide (5c):

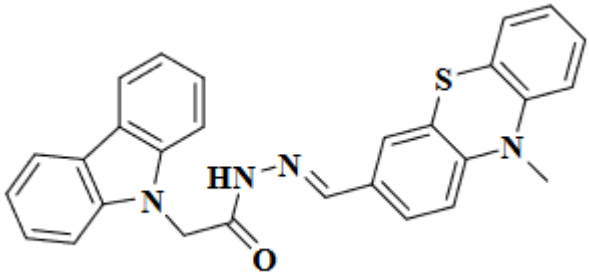
Compound 3a (1 mmol) and 2-(2-oxo-2H-chromen-7- yloxy)acetohydrazide (1 mmol) were added in an equimolar amount to 10 mL of methanol and 0.5 mL of glacial acetic acid. The reaction was then conducted in accordance with the general protocol described in 1.4.4. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 210-212ºC; IR (KBr) vmax: 3448, 3099, 2968,292, 2821, 1730, 1616, 1465, 1408, 1336, 1267, 1157, 1082 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH =11.55 (d, 1H, J = 6.5 Hz, NH), 8.21 (s, 1H, N=CH), 7.91 (s, 1H, C4- ArH of coumarin ring), 6.97-7.72 (m, 10H, Ar-H of coumarin and phenothiazine ring), 6.22 (d, 1H, J = 7.0Hz, C3- Ar-H of coumarin ring), 4.79 (s, 2H, OCH2), 3.34 (s, 3H, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC =168.7, 163.8, 161.2, 160.5, 155.0, 154.9, 153.8, 147.5, 147.0, 144.9, 128.3, 127.7, 126.8, 125.3, 124.8, 123.3, 122.9, 121.9, 115.3, 113.8, 112.8, 111.6, 102.0, 65.8, 35.8; HRMS (EI): m/z [M+] calcd. for C25H19N3O4S: 457.1096; found: 457.1095.



2-(9H-carbazol-9-yl)-N'-((10-methyl-10H-phenothiazin-3-yl)methylene) acetohydrazide (5d):

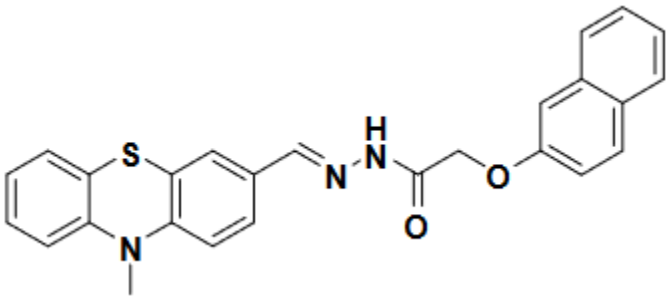
Compound 3a (1 mmol) and 2-(9H-carbazol-9-yl)acetohydrazide (1 mmol) were added in an equimolar amount to 10 mL of methanol and 0.5 mL of glacial acetic acid. The reaction was then conducted in accordance with the general protocol described in 1.4.4. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 173-175ºC; IR (KBr) vmax: 3224, 3072, 2872, 1674, 1598, 1575, 1463, 1382, 1257, 1151 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH = 11.63 (s, 1H, NH), 8.19 (s, 1H, N=CH), 8.16-8.17 (split peaks, 1H, C5- Ar-H of carbazole ring), 7.99 (s, 1H, C4-

Ar-H of carbazole ring), 7.65 (d, 1H, J = 2.0Hz, C1- Ar-H of carbazole ring), 6.98-7.59 (m, 12H, Ar-H of carbazole and phenothiazine ring), 5.17 (s, 2H, NCH2), 3.36 (s, 3H, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC =164.3, 147.2, 147.6, 146.9, 145.6, 144.9, 143.4, 141.3, 129.0, 128.9, 127.9, 127.6, 126.1, 126.0, 125.3, 123.3, 122.7, 121.9, 120.5, 119.5, 119.3, 115.4, 115.1, 115.0, 109.8, 109.8, 44.1, 35.8; HRMS (EI): m/z [M+] calcd. for C28H22N4OS: 462.1514 found: 462.1513.



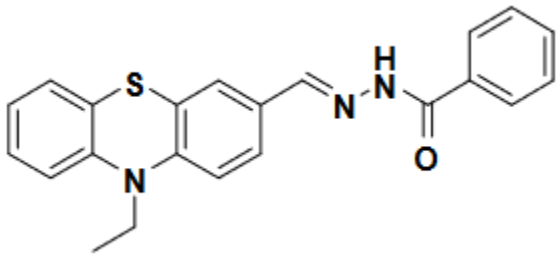
N'-((10-methyl-10H-phenothiazin-3-yl)methylene)-2-(naphthalen-2-yloxy) acetohydrazide (5e):

Compound 3a (1 mmol) and 2-(naphthalen-2-yloxy)acetohydrazide (1 mmol) were added in an equimolar amount to 10 mL of methanol and 0.5 mL of glacial acetic acid. The reaction was then conducted in accordance with the general protocol described in 1.4.4. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 184-186ºC; IR (KBr) vmax: 3271, 3053, 2883, 1672, 1598, 1546, 1462, 1379, 1328, 1255, 1215, 1182, 1083 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH = 11.54 (s, 1H, NH), 8.25 (s, 1H, N=CH), 7.94 (s, 1H, C5- Ar-H of naphthalene ring), 6.99-7.89 (m, 13H, Ar-H of naphthalene and phenothiazine ring), 4.78 (s, 2H, OCH2), 3.32 (s, 3H, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC = 169.2, 156.6, 156.1, 147.4, 147.0, 145.0, 143.3, 134.6, 134.4, 129.8, 128.9, 128.9, 127.4, 127.3, 125.3, 124.9, 124.3, 121.9, 121.9, 119.0, 115.4, 115.1, 115.0, 107.7, 107.5, 65.3, 35.8; HRMS (EI): m/z [M+] calcd. for C26H21N3OS: 439.1354; found: 439.1353.



N'-((10-ethyl-10H-phenothiazin-3-yl)methylene)benzohydrazide (5f):

The reaction was conducted using the general protocol described in 1.4.4 after an equimolar amount of compound 3b (1 mmol) and benzohydrazide (1 mmol) were introduced to 10 mL of methanol and 0.5 mL of glacial acetic acid. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 242-244ºC; IR (KBr) vmax: 3469, 3184, 3024, 2995, 2935, 2862, 1907, 1647, 1573, 1469, 1460, 1398, 1307, 1290, 1242, 1134, 1078 cm-1; 1H NMR (400 MHz, CDCl3, ppm), δH = 11.79 (s, 1H, NH), 8.32(s, 1H, N=CH), 6.95-7.91 (m, 12H, Ar-H of phenothiazine & phenyl ring), 3.96 (q, 2H, J = 7.2 Hz, CH2), 1.32 (t, 3H, J = 6.8 Hz, CH3); 13C NMR (100.612 MHz, CDCl3, ppm), δC = 160.3, 147.1, 143.7, 128.8, 128.6, 128.3, 127.5, 126.6, 123.4, 123.4, 122.4, 116.2, 115.8, 41.5, 13.0; HRMS (EI): m/z [M+] calcd. for C22H19N3OS: 373.1249; found: 373.1248.



N'-((10-ethyl-10H-phenothiazin-3-yl)methylene)isonicotinohydrazide (5g):

Compound 3b (1 mmol) and isonicotinohydrazide (1 mmol) were introduced in an equimolar amount to 10 mL of methanol and 0.5 mL of glacial acetic acid. The reaction was then conducted in accordance with the general protocol provided in 1.4.4. Column chromatographic purification by eluting with hexane/ethyl acetate (3:2) provided the title compound; mp. 203-205ºC; IR (KBr) vmax: 3182, 2995, 2933, 2854, 1651, 1575, 1546, 1460, 1402, 1305, 1242, 1217, 1132, 1072 cm-1; 1H NMR (500 MHz, DMSO-d6, ppm), δH = 11.98 (s, 1H, NH), 8.78 (q, 2H, J = 1.5Hz, C2 & C6- Ar-H of nicotine ring), 8.34 (s, 1H, N=CH), 7.82 (q, 2H, J = 1.5 Hz, C2 & C6- Ar-H of nicotine ring), 7.56 (dd, 2H, J = 2.0 & 3.5Hz, C2 & C4- Ar-H of phenothiazine ring), 7.49 (d, 1H, J = 2.0Hz, C1- Ar-H of phenothiazine ring), 6.95- 7.23 (m, 4H, Ar-H of phenothiazine ring), 3.96 (q, 2H, J = 7.0Hz, CH2), 1.33 (t, 3H, J = 7.0Hz, CH3); 13C NMR (125.757 MHz, DMSO-d6, ppm), δC = 161.8, 150.7, 148.4, 146.5, 143.8, 141.0, 128.7, 128.2, 127.7, 127.5, 125.6, 123.6, 123.3, 122.5, 121.9, 116.1, 115.8, 41.8, 13.0; HRMS (EI): m/z [M+] calcd. for C21H18N4OS: 374.1201; found:374.1200.

5. CONCLUSION

Using UO2(NO3)2.6H2O as a catalyst, a straightforward and effective method for the synthesis of 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives has been presented. This involves a one-pot, three-component condensation of various substituted aldehydes, urea or thiourea, and substituted acetoacetanilides under standard heating and ultrasonic irradiation conditions. The main benefits of this process have been outlined, including low reaction temperatures, quick reaction times, affordable catalysts, simple work-up, and excellent yields. UO2(NO3)2.6H2O and RuCl3 catalysts were used to verify the effects of solvents and the mole percentage of catalyst in order to examine the selectivity and yield. The DPPH radical scavenging method was used to screen the compounds 4a–o for their in vitro antioxidant properties. The synthetic compounds' antibacterial activity was also tested, and it was found that, when compared to a normal medication, various compounds exhibited high to moderate antibacterial activity.

Using an acid catalyst and ordinary heating, ultrasonic, or microwave irradiation, this chapter reports the synthesis of naphthalene substituted Schiff base derivatives 4a-m from 2,2'-(naphthalene-2,7-diylbis(oxy))diacetohydrazide 3 with aromatic/hetero aldehyde. Using the DPPH free radical scavenging technique, the antioxidant activity of the produced compounds was investigated. Only compounds 4e, 4h, and 4i exhibited antioxidant activity, according to the antioxidant investigations; the other compounds lacked any radical scavenging capabilities. Three distinct organisms—S. aureus, E. coli, and P. aeruginosa—were used in an in vitro antibacterial screening process employing the agar well diffusion method. Compounds 4a–m were found to have action that was comparable to that of the common medication, tetracycline.

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